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(54) Title: MACROCYCLIC RIP2 KINASE INHIBITORS

(57) Abstract: The present invention relates to macrocyclic compounds and compositions containing said compounds acting as kinase inhibitors, in particular as inhibitors of RIP2 and/or mutants thereof, for use in the diagnosis, prevention and/or treatment of RIP2-kinase associated diseases. Moreover, the present invention provides methods of using said compounds, for instance as a medicine or diagnostic agent.

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Macrocyclic RIP2 kinase inhibitors

Field of the invention

The present invention relates to macrocyclic compounds and compositions containing said compounds acting as kinase inhibitors, in particular as inhibitors of RIP2, and/or mutants thereof, for use in the diagnosis, prevention and/or treatment of RIP2-kinase associated diseases. Moreover, the present invention provides methods of using said compounds, for instance as a medicine or diagnostic agent.

Background of the invention

Protein kinases constitute a large family of structurally related enzymes that are responsible for the control of a wide variety of signal transduction processes in the cell. They have been shown to be key regulators in most cellular functions including proliferation, cell metabolism, cell survival, apoptosis, DNA damage repair, cell motility... Uncontrolled signalling due to defective control of protein phosphorylation has been implicated in a number of diseases, including, for example, cancer, inflammation, allergies, immune diseases, CNS disorders, angiogenesis...

Amongst the families of protein kinases, one particular example is the Receptor-Interacting Serine/Threonine Kinases including RIP2. RIP2 (Receptor-Interacting Protein 2) is also referred to as Card-Containing Ice-Associated Kinase (CARDIAK), CARD3 (C-terminal CAspase-Recruitment Domain 3), Receptor-Interacting Protein Kinase 2 (RIPK2), or Rip-Like Interacting Clarp Kinase (RICK). RIP2 kinase is composed of an N-terminal kinase domain and a C-terminal caspase-recruitment domain (CARD) linked via an intermediate (IM) region (Curr. Med. Chem. (2005) 4, 35-42)). The CARD domain of RIP2 kinase mediates interaction with other CARD-containing proteins, such as the Nucleotide Oligomerization Domain Proteins, NOD1 and NOD2 (J. Biol. Chem. (2000) 275, 27823-27831 and EMBO reports (2001) 2, 736-742). NOD1 and NOD2 are cytoplasmic receptors which are activated by specific bacterial peptidoglycan motifs and play a key role in innate immune surveillance. Upon intracellular bacterial exposure, NOD1 or NOD2 binds to the protein kinase RIP2 to coordinate NF-κB (nuclear factor κ B)-mediated cytokine responses. Once associated with NOD1/2, RIP2 undergoes autophosphorylation on Tyr 474 (Y474), and acts as a molecular scaffold to bring together other kinases (TAK1, IKK$\alpha/\beta/\gamma$) involved in NF-κB and MAPK activation (Nature Reviews Immunology (2006) 6, 9-20).

Both NOD1/2 and RIP2 are NF-κB regulated genes, and as such, their activation causes a positive feedback loop in which activation of NOD1/2:RIP2 stimulates further activation and further inflammation. Additionally, NOD1/2 and RIP2 expression are stimulated by a variety of mediators of inflammation, including TNF (Tumor Necrosis Factor) and IFN (Interferon). In addition to NF-κB pathway activation, the NOD1/2:RIP2 complex stimulates autophagy, bacteriocidal activity, MHC Class II presentation and MAPK (Mitogen-Activated Protein Kinase) activation. Overall, this pathway modulates the innate immune system to help tailor the adaptive immune response to eradicate the offending pathogen.

Dysregulation of RIP2-dependent signaling has been linked to autoinflammatory diseases. Patients with loss-of-function NOD2 alleles are prone to the development of Crohn's disease, an inflammatory disorder of the gastrointestinal tract (Am. J. Hum. Genet. (2002) 70, 845-857 and Microbes and Infection (2009) 11, 912-918). In contrast, gain-of-function NOD2 mutations have been genetically linked to other inflammatory diseases, such as Blau Syndrome/Early Onset Sarcoidosis (EOS), a pediatric granulomateous disease characterized by uveitis, dermatitis, and arthritis (Nature Genetics (2001) 29, 19-20 and Current Rheumatology Reports (2005) 7, 427-433). Mutations in NOD1 have been associated with asthma (Hum. Mol. Genet. (2005) 14, 935-941), and early-onset and extra-intestinal inflammatory bowel disease (Hum. Mol. Genet. (2005) 14, 1245-1250). Genetic and functional studies have also suggested a role for RIP2-dependent signaling in a variety of other granulomateous disorders, such as sarcoidosis (Journal of Clinical Immunology (2009) 29, 78-89) and Wegner's Granulomatosis (Diagnostic Pathology (2009) 4, 23).

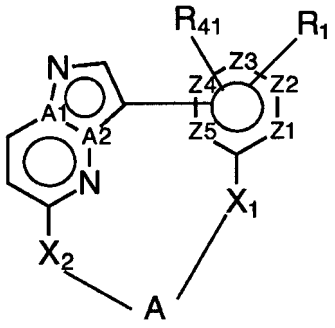
The fact that both loss-of-function polymorphisms and gain-of-function mutations cause inflammatory diseases is likely due to the fact that NOD2 functions as a rheostat to help maintain normal immunologic homeostasis. Lack of coordination between inflammatory signaling pathways influences the development of inflammatory disorders, and the NOD1/2:RIP2 activation equilibrium is central to this coordination. Treatments for Crohn's disease and sarcoidosis currently rely on broad, non-specific immunologic inhibition (e.g., corticosteroids) or on specific cytokine inhibition (e.g., anti-TNF therapies) with significant costs and side effects. Treatment is less than ideal, however, because not all agents are equally efficacious, the diseases occur over long time frames, and not all agents remain efficacious in the same patient. The RIP2 Y474 autophosphorylation event has been shown to be necessary for effective NOD2 signaling and does not occur in the presence of the most common loss-of-function Crohn's disease-associated NOD2 allele. This autophosphorylation is inhibited by non highly selective kinase inhibitors, gefitinib and erlotinib, suggesting that RIP2's tyrosine kinase activity could be targeted specifically in the treatment of inflammatory diseases (Genes Dev. (2010) 1, 2666-77). Several clinical cases were reported about gefitinib or erlotinib treatment being efficient to clear psoriasis or reduce arthritic symptoms or insulin-resistant type 2 diabetes associated with metabolic syndrome (The Oncologist (2013) 18: e3–e5). In mouse established models of chronic inflammatory bowel diseases, inhibition of RIP2 activity by the small molecule SB203580 is efficacious to reduce induced-colitis (J Biol Chem. (2005) 15, 14981-14988.). None of these small molecules however, primarily and selectively targets RIP2. It was therefore an object of the present invention to provide a potent, selective, small molecule inhibitor of RIP2 kinase activity which can block specifically RIP2-dependent pro-inflammatory signaling and thereby provides a therapeutic benefit in autoinflammatory diseases characterized in increased and/or dysregulated RIP2 kinase activity.

We have now found that the macrocyclic pyrazolopyrimidines and imidazopyridazines and pharmaceutically acceptable compositions according to this invention are useful for the treatment of inflammatory disorders, in particular Crohn's disease, bowel disease, Sarcoidosis, psoriasis, rheumatoid arthritis, asthma and insulin-resistant type 2 diabetes, ulcerative colitis, lupus, uveitis, blau syndrome, granulomatous inflammation, in particular behçet's disease, multiple sclerosis, and disease associated with RIP2 kinase activity (i.e. RIP2-kinase associated diseases).

SUMMARY OF THE INVENTION

We have surprisingly found that the macrocyclic compounds described herein act as RIP2 kinase inhibitors, and are thus very useful in the diagnosis, prevention and/or treatment of RIP2-kinase associated diseases.

In a first objective the present invention provides a compound of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof,



I

Wherein

A_1 and A_2 are selected from C and N; wherein when A_1 is C, then A_2 is N; and wherein when A_2 is C, then A_1 is N;

R_1 and R_{41} are each independently selected from –H, –halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -NR_9R_{10}, -(C=O)-R_4, -(C=S)-R_4, -SO_2-R_4, -CN, -NR_9-SO_2-R_4, -C_{3-6}cycloalkyl, -Ar_7 and –Het_1; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, -$NR_{11}R_{12}$, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;

R_2 is selected from –H, -halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -(C=O)-C_{1-6}alkyl, -(C=S)-C_{1-6}alkyl, -(C=O)-O-C_{1-6}alkyl, -(C=S)-O-C_{1-6}alkyl, -(C=O)-$NR_{27}R_{28}$, -(C=S)-$NR_{27}R_{28}$, -C_{3-6}cycloalkyl, -Het_3, -Ar_2, -(C=O)-Het_3, -(C=S)-Het_3, -(C=O)-Ar_2, -(C=S)-Ar_2, -(C=O)-C_{3-6}cycloalkyl, -(C=S)-C_{3-6}cycloalkyl, and -SO_2-C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_3, -Ar_2, and -$NR_{13}R_{14}$;

R_3 is selected from –H, -halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -(C=O)-C_{1-6}alkyl, -(C=S)-C_{1-6}alkyl, -(C=O)-O-C_{1-6}alkyl, -(C=S)-O-C_{1-6}alkyl, -(C=O)-$NR_{29}R_{30}$, -(C=S)-$NR_{29}R_{30}$, -C_{3-6}cycloalkyl -Het_2, -Ar_3, -(C=O)-Het_2, -(C=S)-Het_2, -(C=O)-Ar_3, -(C=S)-Ar_3, -(C=O)-C_{3-6}cycloalkyl, -(C=S)-C_{3-6}cycloalkyl and -SO_2-C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently

substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Het_2, -Ar_3, and -$NR_{15}R_{16}$;

R_4 is independently selected from –halo, –OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -$NR_{17}R_{18}$, -C_{3-6}cycloalkyl, -Ar_8 and -Het_4;

R_5 and R_7 are each independently selected from –H, -OH, -halo, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_9, -Ar_1, -C_{3-6}cycloalkyl, -SO_2-Ar_1, -SO_2, -SO_2-C_{1-6}alkyl, -(C=O), -(C=O)-C_{1-6}alkyl, -(C=S), -(C=S)-C_{1-6}alkyl, -O-(C=O)-C_{1-6}alkyl, -O-(C=S)-C_{1-6}alkyl, -(C=O)-O-C_{1-6}alkyl, and -(C=S)-O-C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Ar_1, -Het_9, and -$NR_{23}R_{24}$;

R_6 is selected from -C_{1-6}alkyl, -SO_2, -SO_2-C_{1-6}alkyl, -SO_2-C_{3-6}cycloalkyl, -(C=O), -(C=O)-C_{1-6}alkyl, -(C=O)-C_{2-6}alkenyl, -(C=O)-O-C_{1-6}alkyl, -(C=O)-Het_6, -(C=O)-Ar_6, -(C=O)-C_{3-6}cycloalkyl, -(C=O)-$NR_{31}R_{32}$, -(C=O)-NR_{31}-(C=O)-R_{32}, -(C=S), -(C=S)-C_{1-6}alkyl, -(C=S)-C_{2-6}alkenyl, -(C=S)-O-C_{1-6}alkyl, -(C=S)-Het_6, -(C=S)-Ar_6, -(C=S)-C_{3-6}cycloalkyl, -(C=S)-$NR_{31}R_{32}$, -(C=S)-NR_{31}-(C=S)-R_{32}, -Het_6, -Ar_6, and -C_{3-6}cycloalkyl;

wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from =O, –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Het_6, -Ar_6, -$NR_{25}R_{26}$, -(C=O)-$NR_{25}R_{26}$, -NR_{33}(C=O)-$NR_{25}R_{26}$, -(C=S)-$NR_{25}R_{26}$, and -NR_{33}(C=S)-$NR_{25}R_{26}$; and

wherein each of said -C_{3-6}cycloalkyl is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl, =O, –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_{12}, -Ar_{11}, and –$NR_{53}R_{54}$, -(C=O)-$NR_{53}R_{54}$, -NR_{55}(C=O)-$NR_{53}R_{54}$, -(C=S)-$NR_{53}R_{54}$, and -NR_{55}(C=S)-$NR_{53}R_{54}$;

R_8 is selected from –NR_{34}-(C=O)-R_{35}, –NR_{34}-(C=S)-R_{35}, -NR_{36}-(C=O)-$NR_{34}R_{35}$, -NR_{36}-(C=S)-$NR_{34}R_{35}$, -NR_{34}-(SO_2)-R_{35}, -NR_{34}-(C=O)-O-R_{35}, -NR_{34}-(C=S)-O-R_{35}, -O-(C=O)-$NR_{34}R_{35}$, and -O-(C=S)-$NR_{34}R_{35}$;

R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, R_{29}, R_{30}, R_{31}, R_{32}, R_{33}, R_{34}, R_{35}, R_{36}, R_{37}, R_{38}, R_{39}, R_{40}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, R_{49}, R_{50}, R_{53}, R_{54} and R_{55} are each independently selected from –H, -halo, =O, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Ar_5 and –Het_7; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Het_7, -Ar_5 and –$NR_{51}R_{52}$;

R_{51} and R_{52} are each independently selected from –H, -halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Ar_{10} and –Het_{10};

R_{42} is selected from -H, -OH, -halo, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -$NR_{46}R_{47}$, -C_{3-6}cycloalkyl, -Ar_9 and -Het_8;

R_{43} is selected from –H -C_{1-6}alkyl, and -C_{3-6}cycloalkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_5, -C_{3-6}cycloalkyl –Ar_4, and –$NR_{44}R_{45}$;

A is selected from -$(CH_2)_n$-Y-$(CH_2)_m$-, –(C=O)-, –(C=S)-, -(C=N)-R_{49}-, -(SO_2)-, -SO_2-NR_5-, -(C=O)-NR_5-, -(C=S)-NR_5-, -NR_5-(C=O)-NR_7-, -NR_5-(C=S)-NR_7-, -NR_6,-, -NR_5-(C=O)-O-, -NR_5-(C=S)-O-, and -CHR_8-;

X_1 is selected from –C_{1-6}alkyl-, –O-C_{1-6}alkyl-, –S-C_{1-6}alkyl-, -(C=O)-, -NR_3-(C=O)-, -C_{1-6}alkyl-NR_3-, -NR_3-, -(C=O)-, -NR_3-(C=O)-NR_{48}-, -NR_3-C_{1-6}alkyl-, -NR_3-SO_2-, -NR_3-(C=O)-C_{1-6}alkyl-, -(C=O)-NR_3-C_{1-6}alkyl-, –O-C_{1-6}alkyl-O-C_{1-6}alkyl- and -C_{1-6}alkyl-NR_3-C_{1-6}alkyl-; wherein each of said -C_{1-6}alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -phenyl, and -$NR_{37}R_{38}$;

X_2 is selected from –C_{1-6}alkyl-, –O-C_{1-6}alkyl-, –S-C_{1-6}alkyl-, -(C=O)-, -NR_2-(C=O)-, -C_{1-6}alkyl-NR_2-, -NR_2-, -(C=O)-, -NR_2-(C=O)-NR_{50}-, -NR_2-C_{1-6}alkyl-, -NR_2-SO_2-, -NR_2-(C=O)-C_{1-6}alkyl-, -(C=O)-NR_2-C_{1-6}alkyl-, –O-C_{1-6}alkyl-O-C_{1-6}alkyl- and -C_{1-6}alkyl-NR_2-C_{1-6}alkyl-; wherein each of said -C_{1-6}alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -phenyl and -$NR_{39}R_{40}$;

Y is selected from a direct bond, -CHR_{42}-, -O-, -S-, and –NR_{43}-;

Ar_1, Ar_2, Ar_3, Ar_4, Ar_5, Ar_6, Ar_7, Ar_8, Ar_9, Ar_{10} and Ar_{11} are each independently a 5- to 10-membered aromatic heterocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of said Ar_1, Ar_2, Ar_3, Ar_4, Ar_5, Ar_6, Ar_7, Ar_8, Ar_9, and Ar_{10} being optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, and –$NR_{19}R_{20}$; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 -halo;

Het_1, Het_2, Het_3, Het_4, Het_5, Het_6, Het_7, Het_8, Het_9, Het_{10}, and Het_{12} are each independently a 4- to 10-membered heterocycle having from 1 to 3 heteroatoms selected from O, N and S, wherein each of said Het_1, Het_2, Het_3, Het_4, Het_5, Het_6, Het_7, Het_8, Het_9, Het_{10}, and Het_{12} is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, –C_{1-6}alkyl, -OC_{1-6}alkyl, -SC_{1-6}alkyl, =O, -(C=O)-C_{1-6}alkyl, and -$NR_{21}R_{22}$; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 -halo;

Z_1, Z_2, Z_3, Z_4 and Z_5 are each independently selected from C and N; and

m and n are each independently 1, 2, 3, or 4;

for use in the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease.

In a first embodiment the present invention provides a compound of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, wherein

A_1 is C and A_2 is N;

R_1 and R_{41} are each independently selected from –H, –halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -NR_9R_{10}, -(C=O)-R_4, -(C=S)-R_4, -SO_2-R_4, -CN, -NR_9-SO_2-R_4, -C_{3-6}cycloalkyl, -Ar_7 and –Het_1; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, -$NR_{11}R_{12}$, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;

R_2 is selected from –H, -halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -(C=O)-C_{1-6}alkyl, -(C=S)-C_{1-6}alkyl, -(C=O)-O-C_{1-6}alkyl, -(C=S)-O-C_{1-6}alkyl, -(C=O)-$NR_{27}R_{28}$, -(C=S)-$NR_{27}R_{28}$, -C_{3-6}cycloalkyl,

-Het_3, -Ar_2, -(C=O)-Het_3, -(C=S)-Het_3, -(C=O)-Ar_2, -(C=S)-Ar_2, -(C=O)-C_{3-6}cycloalkyl, -(C=S)-C_{3-6}cycloalkyl, and -SO_2-C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_3, -Ar_2, and -$NR_{13}R_{14}$;

R_3 is selected from –H, -halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -(C=O)-C_{1-6}alkyl, -(C=S)-C_{1-6}alkyl, -(C=O)-O-C_{1-6}alkyl, -(C=S)-O-C_{1-6}alkyl, -(C=O)-$NR_{29}R_{30}$, -(C=S)-$NR_{29}R_{30}$, -C_{3-6}cycloalkyl -Het_2, -Ar_3, -(C=O)-Het_2, -(C=S)-Het_2, -(C=O)-Ar_3, -(C=S)-Ar_3, -(C=O)-C_{3-6}cycloalkyl, -(C=S)-C_{3-6}cycloalkyl and -SO_2-C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Het_2, -Ar_3, and -$NR_{15}R_{16}$;

R_4 is independently selected from –halo, –OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -$NR_{17}R_{18}$, -C_{3-6}cycloalkyl, -Ar_8 and -Het_4;

R_5 and R_7 are each independently selected from –H, -OH, -halo, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_9, -Ar_1, -C_{3-6}cycloalkyl, -SO_2-Ar_1, -SO_2, -SO_2-C_{1-6}alkyl, -(C=O), -(C=O)-C_{1-6}alkyl, -(C=S), -(C=S)-C_{1-6}alkyl, -O-(C=O)-C_{1-6}alkyl, -O-(C=S)-C_{1-6}alkyl, -(C=O)-O-C_{1-6}alkyl, and -(C=S)-O-C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Ar_1, -Het_9, and -$NR_{23}R_{24}$;

R_6 is selected from -C_{1-6}alkyl, -SO_2, -SO_2-C_{1-6}alkyl, -SO_2-C_{3-6}cycloalkyl, -(C=O), -(C=O)-C_{1-6}alkyl, -(C=O)-C_{2-6}alkenyl, -(C=O)-O-C_{1-6}alkyl, -(C=O)-Het_6, -(C=O)-Ar_6, -(C=O)-C_{3-6}cycloalkyl, -(C=O)-$NR_{31}R_{32}$, -(C=O)-NR_{31}-(C=O)-R_{32}, -(C=S), -(C=S)-C_{1-6}alkyl, -(C=S)-C_{2-6}alkenyl, -(C=S)-O-C_{1-6}alkyl, -(C=S)-Het_6, -(C=S)-Ar_6, -(C=S)-C_{3-6}cycloalkyl, -(C=S)-$NR_{31}R_{32}$, -(C=S)-NR_{31}-(C=S)-R_{32}, -Het_6, -Ar_6, and -C_{3-6}cycloalkyl;

wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from =O, –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Het_6, -Ar_6, -$NR_{25}R_{26}$, -(C=O)-$NR_{25}R_{26}$, -NR_{33}(C=O)-$NR_{25}R_{26}$, -(C=S)-$NR_{25}R_{26}$, and -NR_{33}(C=S)-$NR_{25}R_{26}$; and

wherein each of said -C_{3-6}cycloalkyl is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl, =O, –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_{12}, -Ar_{11}, and –$NR_{53}R_{54}$, -(C=O)-$NR_{53}R_{54}$, -NR_{55}(C=O)-$NR_{53}R_{54}$, -(C=S)-$NR_{53}R_{54}$, and -NR_{55}(C=S)-$NR_{53}R_{54}$;

R_8 is selected from –NR_{34}-(C=O)-R_{35}, –NR_{34}-(C=S)-R_{35}, -NR_{36}-(C=O)-$NR_{34}R_{35}$, -NR_{36}-(C=S)-$NR_{34}R_{35}$, -NR_{34}-(SO_2)-R_{35}, -NR_{34}-(C=O)-O-R_{35}, -NR_{34}-(C=S)-O-R_{35}, -O-(C=O)-$NR_{34}R_{35}$, and -O-(C=S)-$NR_{34}R_{35}$;

R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, R_{29}, R_{30}, R_{31}, R_{32}, R_{33}, R_{34}, R_{35}, R_{36}, R_{37}, R_{38}, R_{39}, R_{40}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, R_{49}, R_{50}, R_{53}, R_{54} and R_{55} are each independently selected from –H, -halo, =O, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Ar_5 and –Het_7; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Het_7, -Ar_5 and –$NR_{51}R_{52}$;

R_{51} and R_{52} are each independently selected from –H, -halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Ar_{10} and –Het_{10};

R_{42} is selected from -H, -OH, -halo, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -$NR_{46}R_{47}$, -C_{3-6}cycloalkyl, -Ar_9 and -Het_8;

R_{43} is selected from –H -C_{1-6}alkyl, and -C_{3-6}cycloalkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_5, -C_{3-6}cycloalkyl –Ar_4, and –$NR_{44}R_{45}$;

A is selected from -$(CH_2)_n$-Y-$(CH_2)_m$-, –(C=O)-, –(C=S)-, -(C=N)-R_{49}-, -(SO_2)-, -SO_2-NR_5-, -(C=O)-NR_5-, -(C=S)-NR_5-, -NR_5-(C=O)-NR_7-, -NR_5-(C=S)-NR_7-, -NR_6,-, -NR_5-(C=O)-O-, -NR_5-(C=S)-O-, and -CHR_8- ;

X_1 is selected from –C_{1-6}alkyl-, –O-C_{1-6}alkyl-, –S-C_{1-6}alkyl-, -(C=O)-, -NR_3-(C=O)-, -C_{1-6}alkyl-NR_3-, -NR_3-, -(C=O)-, -NR_3-(C=O)-NR_{48}-, -NR_3-C_{1-6}alkyl-, -NR_3-SO_2-, -NR_3-(C=O)-C_{1-6}alkyl-, -(C=O)-NR_3-C_{1-6}alkyl-, –O-C_{1-6}alkyl-O-C_{1-6}alkyl- and -C_{1-6}alkyl-NR_3-C_{1-6}alkyl-; wherein each of said -C_{1-6}alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -phenyl, and -$NR_{37}R_{38}$;

X_2 is selected from –C_{1-6}alkyl-, –O-C_{1-6}alkyl-, –S-C_{1-6}alkyl-, -(C=O)-, -NR_2-(C=O)-, -C_{1-6}alkyl-NR_2-, -NR_2-, -(C=O)-, -NR_2-(C=O)-NR_{50}-, -NR_2-C_{1-6}alkyl-, -NR_2-SO_2-, -NR_2-(C=O)-C_{1-6}alkyl-, -(C=O)-NR_2-C_{1-6}alkyl-, –O-C_{1-6}alkyl-O-C_{1-6}alkyl- and -C_{1-6}alkyl-NR_2-C_{1-6}alkyl-; wherein each of said -C_{1-6}alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -phenyl and -$NR_{39}R_{40}$;

Y is selected from a direct bond, -CHR_{42}-, -O-, -S-, and –NR_{43}-;

Ar_1, Ar_2, Ar_3, Ar_4, Ar_5, Ar_6, Ar_7, Ar_8, Ar_9, Ar_{10} and Ar_{11} are each independently a 5- to 10-membered aromatic heterocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of said Ar_1, Ar_2, Ar_3, Ar_4, Ar_5, Ar_6, Ar_7, Ar_8, Ar_9, and Ar_{10} being optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, and –$NR_{19}R_{20}$; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 -halo;

Het_1, Het_2, Het_3, Het_4, Het_5, Het_6, Het_7, Het_8, Het_9, Het_{10}, and Het_{12} are each independently a 4- to 10-membered heterocycle having from 1 to 3 heteroatoms selected from O, N and S, wherein each of said Het_1, Het_2, Het_3, Het_4, Het_5, Het_6, Het_7, Het_8, Het_9, Het_{10}, and Het_{12} is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, -C_{1-6}alkyl, -OC_{1-6}alkyl, -SC_{1-6}alkyl, =O, -(C=O)-C_{1-6}alkyl, and -$NR_{21}R_{22}$; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 -halo;

Z_1, Z_2, Z_3, Z_4 and Z_5 are each independently selected from C and N; and

m and n are each independently 1, 2, 3, or 4;

for use in the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease.

In a further embodiment, the present invention provides a compound of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, wherein

A_1 is N and A_2 is C

R_1 and R_{41} are each independently selected from –H, –halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -NR_9R_{10}, -(C=O)-R_4, -(C=S)-R_4, -SO_2-R_4, -CN, -NR_9-SO_2-R_4, -C_{3-6}cycloalkyl, -Ar_7 and –Het_1; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, -$NR_{11}R_{12}$, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;

R_2 is selected from –H, -halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -(C=O)-C_{1-6}alkyl, -(C=S)-C_{1-6}alkyl, -(C=O)-O-C_{1-6}alkyl, -(C=S)-O-C_{1-6}alkyl, -(C=O)-$NR_{27}R_{28}$, -(C=S)-$NR_{27}R_{28}$, -C_{3-6}cycloalkyl, -Het_3, -Ar_2, -(C=O)-Het_3, -(C=S)-Het_3, -(C=O)-Ar_2, -(C=S)-Ar_2, -(C=O)-C_{3-6}cycloalkyl, -(C=S)-C_{3-6}cycloalkyl, and -SO_2-C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_3, -Ar_2, and -$NR_{13}R_{14}$;

R_3 is selected from –H, -halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -(C=O)-C_{1-6}alkyl, -(C=S)-C_{1-6}alkyl, -(C=O)-O-C_{1-6}alkyl, -(C=S)-O-C_{1-6}alkyl, -(C=O)-$NR_{29}R_{30}$, -(C=S)-$NR_{29}R_{30}$, -C_{3-6}cycloalkyl -Het_2, -Ar_3, -(C=O)-Het_2, -(C=S)-Het_2, -(C=O)-Ar_3, -(C=S)-Ar_3, -(C=O)-C_{3-6}cycloalkyl, -(C=S)-C_{3-6}cycloalkyl and -SO_2-C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Het_2, -Ar_3, and -$NR_{15}R_{16}$;

R_4 is independently selected from –halo, –OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -$NR_{17}R_{18}$, -C_{3-6}cycloalkyl, -Ar_8 and -Het_4;

R_5 and R_7 are each independently selected from –H, -OH, -halo, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_9, -Ar_1, -C_{3-6}cycloalkyl, -SO_2-Ar_1, -SO_2, -SO_2-C_{1-6}alkyl, -(C=O), -(C=O)-C_{1-6}alkyl, -(C=S), -(C=S)-C_{1-6}alkyl, -O-(C=O)-C_{1-6}alkyl, -O-(C=S)-C_{1-6}alkyl, -(C=O)-O-C_{1-6}alkyl, and -(C=S)-O-C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Ar_1, -Het_9, and -$NR_{23}R_{24}$;

R_6 is selected from -C_{1-6}alkyl, -SO_2, -SO_2-C_{1-6}alkyl, -SO_2-C_{3-6}cycloalkyl, -(C=O), -(C=O)-C_{1-6}alkyl, -(C=O)-C_{2-6}alkenyl, -(C=O)-O-C_{1-6}alkyl, -(C=O)-Het_6, -(C=O)-Ar_6, -(C=O)-C_{3-6}cycloalkyl, -(C=O)-$NR_{31}R_{32}$, -(C=O)-NR_{31}-(C=O)-R_{32}, -(C=S), -(C=S)-C_{1-6}alkyl, -(C=S)-C_{2-6}alkenyl, -(C=S)-O-C_{1-6}alkyl, -(C=S)-Het_6, -(C=S)-Ar_6, -(C=S)-C_{3-6}cycloalkyl, -(C=S)-$NR_{31}R_{32}$, -(C=S)-NR_{31}-(C=S)-R_{32}, -Het_6, -Ar_6, and -C_{3-6}cycloalkyl;

wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from =O, –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Het_6, -Ar_6, -$NR_{25}R_{26}$, -(C=O)-$NR_{25}R_{26}$, -NR_{33}(C=O)-$NR_{25}R_{26}$, -(C=S)-$NR_{25}R_{26}$, and -NR_{33}(C=S)-$NR_{25}R_{26}$; and

wherein each of said -C_{3-6}cycloalkyl is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl, =O, –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_{12}, -Ar_{11}, and –$NR_{53}R_{54}$, -(C=O)-$NR_{53}R_{54}$, -NR_{55}(C=O)-$NR_{53}R_{54}$, -(C=S)-$NR_{53}R_{54}$, and -NR_{55}(C=S)-$NR_{53}R_{54}$;

R_8 is selected from $-NR_{34}-(C=O)-R_{35}$, $-NR_{34}-(C=S)-R_{35}$, $-NR_{36}-(C=O)-NR_{34}R_{35}$, $-NR_{36}-(C=S)-NR_{34}R_{35}$, $-NR_{34}-(SO_2)-R_{35}$, $-NR_{34}-(C=O)-O-R_{35}$, $-NR_{34}-(C=S)-O-R_{35}$, $-O-(C=O)-NR_{34}R_{35}$, and $-O-(C=S)-NR_{34}R_{35}$;

R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, R_{29}, R_{30}, R_{31}, R_{32}, R_{33}, R_{34}, R_{35}, R_{36}, R_{37}, R_{38}, R_{39}, R_{40}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, R_{49}, R_{50}, R_{53}, R_{54} and R_{55} are each independently selected from –H, -halo, =O, -OH, $-C_{1-6}$alkyl, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-C_{3-6}$cycloalkyl, $-Ar_5$ and $-Het_7$; wherein each of said $-C_{1-6}$alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-C_{3-6}$cycloalkyl, $-Het_7$, $-Ar_5$ and $-NR_{51}R_{52}$;

R_{51} and R_{52} are each independently selected from –H, -halo, -OH, $-C_{1-6}$alkyl, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-C_{3-6}$cycloalkyl, $-Ar_{10}$ and $-Het_{10}$;

R_{42} is selected from -H, -OH, -halo, $-C_{1-6}$alkyl, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-NR_{46}R_{47}$, $-C_{3-6}$cycloalkyl, $-Ar_9$ and $-Het_8$;

R_{43} is selected from –H $-C_{1-6}$alkyl, and $-C_{3-6}$cycloalkyl; wherein each of said $-C_{1-6}$alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-Het_5$, $-C_{3-6}$cycloalkyl $-Ar_4$, and $-NR_{44}R_{45}$;

A is selected from $-(CH_2)_n-Y-(CH_2)_m-$, –(C=O)-, –(C=S)-, -(C=N)-R_{49}-, $-(SO_2)-$, $-SO_2-NR_5-$, $-(C=O)-NR_5-$, $-(C=S)-NR_5-$, $-NR_5-(C=O)-NR_7-$, $-NR_5-(C=S)-NR_7-$, $-NR_6-$, $-NR_5-(C=O)-O-$, $-NR_5-(C=S)-O-$, and $-CHR_8-$;

X_1 is selected from $-C_{1-6}$alkyl-, $-O-C_{1-6}$alkyl-, $-S-C_{1-6}$alkyl-, -(C=O)-, $-NR_3-(C=O)-$, $-C_{1-6}$alkyl-NR_3-, $-NR_3-$, -(C=O)-, $-NR_3-(C=O)-NR_{48}-$, $-NR_3-C_{1-6}$alkyl-, $-NR_3-SO_2-$, $-NR_3-(C=O)-C_{1-6}$alkyl-, $-(C=O)-NR_3-C_{1-6}$alkyl-, $-O-C_{1-6}$alkyl-$O-C_{1-6}$alkyl- and $-C_{1-6}$alkyl-NR_3-C_{1-6}alkyl-; wherein each of said $-C_{1-6}$alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, $-C_{1-6}$alkyl, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, -phenyl, and $-NR_{37}R_{38}$;

X_2 is selected from $-C_{1-6}$alkyl-, $-O-C_{1-6}$alkyl-, $-S-C_{1-6}$alkyl-, -(C=O)-, $-NR_2-(C=O)-$, $-C_{1-6}$alkyl-NR_2-, $-NR_2-$, -(C=O)-, $-NR_2-(C=O)-NR_{50}-$, $-NR_2-C_{1-6}$alkyl-, $-NR_2-SO_2-$, $-NR_2-(C=O)-C_{1-6}$alkyl-, $-(C=O)-NR_2-C_{1-6}$alkyl-, $-O-C_{1-6}$alkyl-$O-C_{1-6}$alkyl- and $-C_{1-6}$alkyl-NR_2-C_{1-6}alkyl-; wherein each of said $-C_{1-6}$alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, $-C_{1-6}$alkyl, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, -phenyl and $-NR_{39}R_{40}$;

Y is selected from a direct bond, $-CHR_{42}-$, -O-, -S-, and $-NR_{43}-$;

Ar_1, Ar_2, Ar_3, Ar_4, Ar_5, Ar_6, Ar_7, Ar_8, Ar_9, Ar_{10} and Ar_{11} are each independently a 5- to 10-membered aromatic heterocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of said Ar_1, Ar_2, Ar_3, Ar_4, Ar_5, Ar_6, Ar_7, Ar_8, Ar_9, and Ar_{10} being optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, $-C_{1-6}$alkyl, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, and $-NR_{19}R_{20}$; wherein each of said $-C_{1-6}$alkyl is optionally and independently substituted with from 1 to 3 -halo;

Het_1, Het_2, Het_3, Het_4, Het_5, Het_6, Het_7, Het_8, Het_9, Het_{10}, and Het_{12} are each independently a 4- to 10-membered heterocycle having from 1 to 3 heteroatoms selected from O, N and S, wherein each of said Het_1, Het_2, Het_3, Het_4, Het_5, Het_6, Het_7, Het_8, Het_9, Het_{10}, and Het_{12} is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, $-C_{1-}$

$_6$alkyl, -OC_{1-6}alkyl, -SC_{1-6}alkyl, =O, -(C=O)-C_{1-6}alkyl, and -$NR_{21}R_{22}$; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 -halo;

Z_1, Z_2, Z_3, Z_4 and Z_5 are each independently selected from C and N; and

m and n are each independently 1, 2, 3, or 4;

for use in the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease.

In a further embodiment, the present invention provides a compound of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, wherein

A_1 and A_2 are selected from C and N; wherein when A_1 is C, then A_2 is N; and wherein when A_2 is C, then A_1 is N;

R_1 and R_{41} are each independently selected from –H, –halo, -C_{1-6}alkyl, -(C=O)-R_4, and -CN; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -O-C_{1-6}alkyl;

R_2 is selected from –H, and -C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with -$NR_{13}R_{14}$;

R_3 is selected from –H, and -C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with -$NR_{15}R_{16}$;

R_4 is -$NR_{17}R_{18}$;

R_5 is –H;

R_6 is selected from -C_{1-6}alkyl, -(C=O)-C_{1-6}alkyl, -(C=O)-C_{3-6}cycloalkyl, -Het_6, and -C_{3-6}cycloalkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -O-C_{1-6}alkyl and -Het_6;

and wherein each of said -C_{3-6}cycloalkyl is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl;

R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, are each independently selected from –H, and -C_{1-6}alkyl;

R_{43} is selected from –H, and -C_{1-6}alkyl;

A is selected from -$(CH_2)_n$-Y-$(CH_2)_m$-, -NR_6-, and -(C=O)-NR_5-;

X_1 is selected from –O-C_{1-6}alkyl-, -C_{1-6}alkyl-NR_3-, and -C_{1-6}alkyl-NR_3-C_{1-6}alkyl-; wherein each of said -C_{1-6}alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl;

X_2 is selected from –O-C_{1-6}alkyl-, -C_{1-6}alkyl-NR_2-; wherein each of said -C_{1-6}alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl;

Y is –NR_{43}-;

Het_6 is a 4- to 10-membered heterocycle having from 1 to 3 heteroatoms selected from O, N and S;

Z_1, Z_2, Z_3, Z_4 and Z_5 are each independently selected from C and N; and

m and n are each independently 1, 2, 3, or 4;

for use in the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease.

In a further embodiment, the present invention provides a compound of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, wherein

A_1 is C and A_2 is N;

R_1 and R_{41} are each independently selected from –H, –halo, -C_{1-6}alkyl, -(C=O)-R_4, and -CN; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -O-C_{1-6}alkyl;

R_2 is selected from –H, and -C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with -$NR_{13}R_{14}$;

R_3 is selected from –H, and -C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with -$NR_{15}R_{16}$;

R_4 is -$NR_{17}R_{18}$;

R_5 is –H;

R_6 is selected from -C_{1-6}alkyl, -(C=O)-C_{1-6}alkyl, -(C=O)-C_{3-6}cycloalkyl, -Het_6, and -C_{3-6}cycloalkyl;

wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -O-C_{1-6}alkyl and -Het_6;

and wherein each of said -C_{3-6}cycloalkyl is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl;

R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, are each independently selected from –H, and -C_{1-6}alkyl;

R_{43} is selected from –H, and -C_{1-6}alkyl;

A is selected from -$(CH_2)_n$-Y-$(CH_2)_m$-, -NR_6-, and -(C=O)-NR_5- ;

X_1 is selected from –O-C_{1-6}alkyl-, -C_{1-6}alkyl-NR_3-, and -C_{1-6}alkyl-NR_3-C_{1-6}alkyl-; wherein each of said -C_{1-6}alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl;

X_2 is selected from –O-C_{1-6}alkyl-, -C_{1-6}alkyl-NR_2-; wherein each of said -C_{1-6}alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl;

Y is -NR_{43}-;

Het_6 is a 4- to 10-membered heterocycle having from 1 to 3 heteroatoms selected from O, N and S;

Z_1, Z_2, Z_3, Z_4 and Z_5 are each independently selected from C and N; and

m and n are each independently 1, 2, 3, or 4;

for use in the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease.

In a further embodiment, the present invention provides a compound of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, wherein

A_1 is N and A_2 is C;

R_1 and R_{41} are each independently selected from –H, –halo, -C_{1-6}alkyl, -(C=O)-R_4, and -CN; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -O-C_{1-6}alkyl;

R_2 is selected from –H, and -C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with -$NR_{13}R_{14}$;

R_3 is selected from –H, and -C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with -$NR_{15}R_{16}$;

R_4 is -$NR_{17}R_{18}$;

R_5 is –H;

R_6 is selected from -C_{1-6}alkyl, -(C=O)-C_{1-6}alkyl, -(C=O)-C_{3-6}cycloalkyl, -Het_6, and -C_{3-6}cycloalkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -O-C_{1-6}alkyl and -Het_6;
and wherein each of said -C_{3-6}cycloalkyl is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl;

R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, are each independently selected from –H, and -C_{1-6}alkyl;

R_{43} is selected from –H, and -C_{1-6}alkyl;

A is selected from -$(CH_2)_n$-Y-$(CH_2)_m$-, and -NR_6-, -(C=O)-NR_5- ;

X_1 is selected from –O-C_{1-6}alkyl-, -C_{1-6}alkyl-NR_3-, and -C_{1-6}alkyl-NR_3-C_{1-6}alkyl-; wherein each of said -C_{1-6}alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl;

X_2 is selected from –O-C_{1-6}alkyl-, -C_{1-6}alkyl-NR_2-; wherein each of said -C_{1-6}alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl;

Y is –NR_{43}-;

Het_6 is a 4- to 10-membered heterocycle having from 1 to 3 heteroatoms selected from O, N and S;

Z_1, Z_2, Z_3, Z_4 and Z_5 are each independently selected from C and N; and

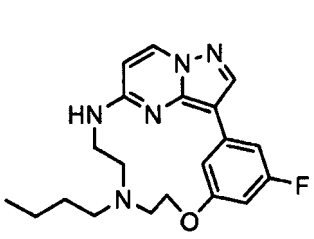
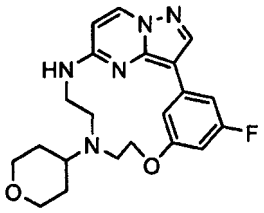
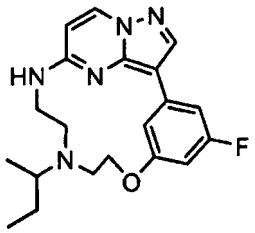
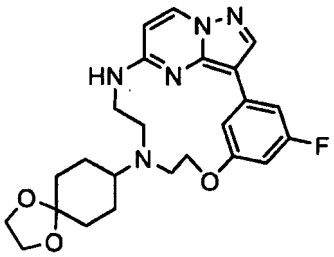
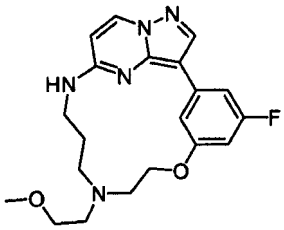
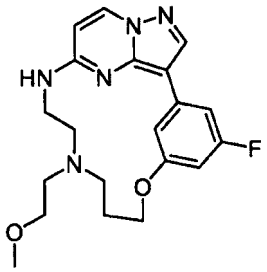
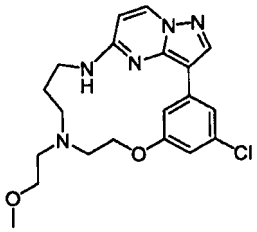
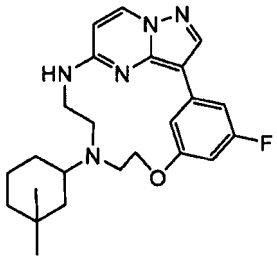
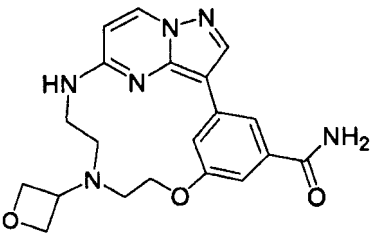
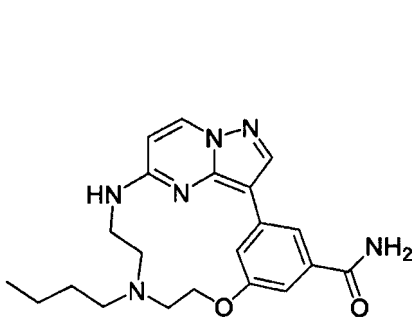
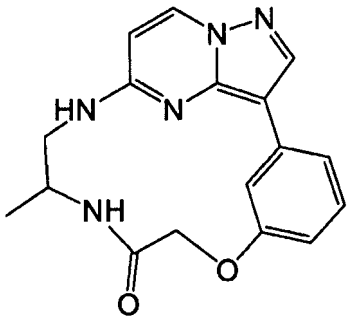
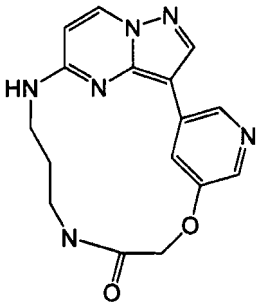
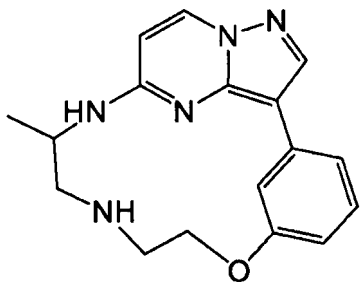
m and n are each independently 1, 2, 3, or 4;

for use in the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease.

In a further aspect, the present invention provides a compound according to the present invention for use in the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease; wherein the pyrazolopyrimidine or the imidazopyridazine moiety is linked to the aryl or heteroaryl moiety at position Z_4 or Z_5, in accordance with the numbering as provided in Formula I.

In yet a further aspect, the present invention provides a compound according to the present invention for use in the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease; wherein R_1 is linked to the aryl or heteroaryl moiety at position Z_1, Z_2 or Z_3, in accordance with the numbering as provided in Formula I.

In yet a further aspect, the present invention provides a compound selected from the list comprising:

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In a particular embodiment, the RIP2-kinase associated disease is an inflammatory disorder, more in particular Crohn's disease, bowel disease, Sarcoidosis, psoriasis, rheumatoid arthritis, asthma, ulcerative colitis, lupus, uveitis, blau syndrome, granulomatous inflammation, in particular behçet's disease, multiple sclerosis and insulin-resistant type 2 diabetes.

The present invention further provides a pharmaceutical composition for use in the prevention and/or treatment of a RIP2-kinase associated disease comprising a compound according to this invention.

Furthermore, the present invention provides the use of a compound or composition according to this invention, suitable for inhibiting the activity of a kinase; in particular a RIP2 kinase; or for the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease.

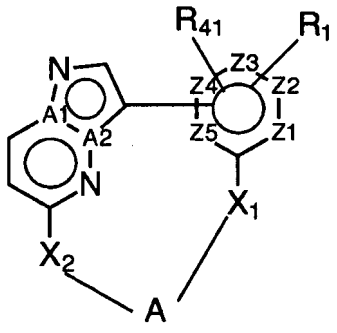
Finally, the present invention provides a method for prevention and/or treatment of a RIP2-kinase associated disease; said method comprising administering to a subject in need thereof a compound or a composition according to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention will now be further described. In the following passages, different aspects of the invention are defined in more detail. Each aspect so defined may be combined with any other aspect or aspects unless clearly indicated to the contrary. In particular, any feature indicated as being preferred or advantageous may be combined with any other feature or features indicated as being preferred or advantageous.

Unless a context dictates otherwise, asterisks are used herein to indicate the point at which a mono- or bivalent radical depicted is connected to the structure to which it relates and of which the radical forms part.

As already mentioned hereinbefore, in a first aspect the present invention provides a compound of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof,



I

Wherein

A_1 and A_2 are selected from C and N; wherein when A_1 is C, then A_2 is N; and wherein when A_2 is C, then A_1 is N;

R_1 and R_{41} are each independently selected from –H, –halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -NR_9R_{10}, -(C=O)-R_4, -(C=S)-R_4, -SO_2-R_4, -CN, -NR_9-SO_2-R_4, -C_{3-6}cycloalkyl, -Ar_7 and –Het_1; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, -$NR_{11}R_{12}$, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;

R_2 is selected from –H, -halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -(C=O)-C_{1-6}alkyl, -(C=S)-C_{1-6}alkyl, -(C=O)-O-C_{1-6}alkyl, -(C=S)-O-C_{1-6}alkyl, -(C=O)-$NR_{27}R_{28}$, -(C=S)-$NR_{27}R_{28}$, -C_{3-6}cycloalkyl, -Het_3, -Ar_2, -(C=O)-Het_3, -(C=S)-Het_3, -(C=O)-Ar_2, -(C=S)-Ar_2, -(C=O)-C_{3-6}cycloalkyl, -(C=S)-C_{3-6}cycloalkyl, and -SO_2-C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_3, -Ar_2, and -$NR_{13}R_{14}$;

R_3 is selected from –H, -halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -(C=O)-C_{1-6}alkyl, -(C=S)-C_{1-6}alkyl, -(C=O)-O-C_{1-6}alkyl, -(C=S)-O-C_{1-6}alkyl, -(C=O)-$NR_{29}R_{30}$, -(C=S)-$NR_{29}R_{30}$, -C_{3-6}cycloalkyl -Het_2, -Ar_3, -(C=O)-Het_2, -(C=S)-Het_2, -(C=O)-Ar_3, -(C=S)-Ar_3, -(C=O)-C_{3-6}cycloalkyl, -(C=S)-C_{3-6}cycloalkyl and -SO_2-C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Het_2, -Ar_3, and -$NR_{15}R_{16}$;

R_4 is independently selected from –halo, –OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -$NR_{17}R_{18}$, -C_{3-6}cycloalkyl, -Ar_8 and -Het_4;

R_5 and R_7 are each independently selected from –H, -OH, -halo, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_9, -Ar_1, -C_{3-6}cycloalkyl, -SO_2-Ar_1, -SO_2, -SO_2-C_{1-6}alkyl, -(C=O), -(C=O)-C_{1-6}alkyl, -(C=S), -(C=S)-C_{1-6}alkyl, -O-(C=O)-C_{1-6}alkyl, -O-(C=S)-C_{1-6}alkyl, -(C=O)-O-C_{1-6}alkyl, and -(C=S)-O-C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Ar_1, -Het_9, and -$NR_{23}R_{24}$;

R_6 is selected from -C_{1-6}alkyl, -SO_2, -SO_2-C_{1-6}alkyl, -SO_2-C_{3-6}cycloalkyl, -(C=O), -(C=O)-C_{1-6}alkyl, -(C=O)-C_{2-6}alkenyl, -(C=O)-O-C_{1-6}alkyl, -(C=O)-Het_6, -(C=O)-Ar_6, -(C=O)-C_{3-6}cycloalkyl, -(C=O)-$NR_{31}R_{32}$, -(C=O)-NR_{31}-(C=O)-R_{32}, -(C=S), -(C=S)-C_{1-6}alkyl, -(C=S)-C_{2-6}alkenyl, -(C=S)-O-C_{1-6}alkyl, -(C=S)-Het_6, -(C=S)-Ar_6, -(C=S)-C_{3-6}cycloalkyl, -(C=S)-$NR_{31}R_{32}$, -(C=S)-NR_{31}-(C=S)-R_{32}, -Het_6, -Ar_6, and -C_{3-6}cycloalkyl;

wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from =O, –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Het_6, -Ar_6, -$NR_{25}R_{26}$, -(C=O)-$NR_{25}R_{26}$, -NR_{33}(C=O)-$NR_{25}R_{26}$, -(C=S)-$NR_{25}R_{26}$, and -NR_{33}(C=S)-$NR_{25}R_{26}$; and

wherein each of said -C_{3-6}cycloalkyl is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl, =O, –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_{12}, -Ar_{11}, and –$NR_{53}R_{54}$, -(C=O)-$NR_{53}R_{54}$, -NR_{55}(C=O)-$NR_{53}R_{54}$, -(C=S)-$NR_{53}R_{54}$, and -NR_{55}(C=S)-$NR_{53}R_{54}$;

R_8 is selected from $-NR_{34}-(C=O)-R_{35}$, $-NR_{34}-(C=S)-R_{35}$, $-NR_{36}-(C=O)-NR_{34}R_{35}$, $-NR_{36}-(C=S)-NR_{34}R_{35}$, $-NR_{34}-(SO_2)-R_{35}$, $-NR_{34}-(C=O)-O-R_{35}$, $-NR_{34}-(C=S)-O-R_{35}$, $-O-(C=O)-NR_{34}R_{35}$, and $-O-(C=S)-NR_{34}R_{35}$;

R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, R_{29}, R_{30}, R_{31}, R_{32}, R_{33}, R_{34}, R_{35}, R_{36}, R_{37}, R_{38}, R_{39}, R_{40}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, R_{49}, R_{50}, R_{53}, R_{54} and R_{55} are each independently selected from –H, -halo, =O, -OH, $-C_{1-6}$alkyl, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-C_{3-6}$cycloalkyl, $-Ar_5$ and $-Het_7$; wherein each of said $-C_{1-6}$alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-C_{3-6}$cycloalkyl, $-Het_7$, $-Ar_5$ and $-NR_{51}R_{52}$;

R_{51} and R_{52} are each independently selected from –H, -halo, -OH, $-C_{1-6}$alkyl, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-C_{3-6}$cycloalkyl, $-Ar_{10}$ and $-Het_{10}$;

R_{42} is selected from -H, -OH, -halo, $-C_{1-6}$alkyl, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-NR_{46}R_{47}$, $-C_{3-6}$cycloalkyl, $-Ar_9$ and $-Het_8$;

R_{43} is selected from –H $-C_{1-6}$alkyl, and $-C_{3-6}$cycloalkyl; wherein each of said $-C_{1-6}$alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-Het_5$, $-C_{3-6}$cycloalkyl $-Ar_4$, and $-NR_{44}R_{45}$;

A is selected from $-(CH_2)_n-Y-(CH_2)_m-$, –(C=O)-, –(C=S)-, -(C=N)-R_{49}-, $-(SO_2)-$, $-SO_2-NR_5-$, -(C=O)-NR_5-, -(C=S)-NR_5-, $-NR_5-(C=O)-NR_7-$, $-NR_5-(C=S)-NR_7-$, $-NR_6-$, $-NR_5-(C=O)-O-$, $-NR_5-(C=S)-O-$, and $-CHR_8-$;

X_1 is selected from $-C_{1-6}$alkyl-, $-O-C_{1-6}$alkyl-, $-S-C_{1-6}$alkyl-, -(C=O)-, $-NR_3-(C=O)-$, $-C_{1-6}$alkyl-NR_3-, $-NR_3-$, -(C=O)-, $-NR_3-(C=O)-NR_{48}-$, $-NR_3-C_{1-6}$alkyl-, $-NR_3-SO_2-$, $-NR_3-(C=O)-C_{1-6}$alkyl-, -(C=O)-NR_3-C_{1-6}alkyl-, $-O-C_{1-6}$alkyl-$O-C_{1-6}$alkyl- and $-C_{1-6}$alkyl-NR_3-C_{1-6}alkyl-; wherein each of said $-C_{1-6}$alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, $-C_{1-6}$alkyl, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, -phenyl, and $-NR_{37}R_{38}$;

X_2 is selected from $-C_{1-6}$alkyl-, $-O-C_{1-6}$alkyl-, $-S-C_{1-6}$alkyl-, -(C=O)-, $-NR_2-(C=O)-$, $-C_{1-6}$alkyl-NR_2-, $-NR_2-$, -(C=O)-, $-NR_2-(C=O)-NR_{50}-$, $-NR_2-C_{1-6}$alkyl-, $-NR_2-SO_2-$, $-NR_2-(C=O)-C_{1-6}$alkyl-, -(C=O)-NR_2-C_{1-6}alkyl-, $-O-C_{1-6}$alkyl-$O-C_{1-6}$alkyl- and $-C_{1-6}$alkyl-NR_2-C_{1-6}alkyl-; wherein each of said $-C_{1-6}$alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, $-C_{1-6}$alkyl, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, -phenyl and $-NR_{39}R_{40}$;

Y is selected from a direct bond, $-CHR_{42}-$, -O-, -S-, and $-NR_{43}-$;

Ar_1, Ar_2, Ar_3, Ar_4, Ar_5, Ar_6, Ar_7, Ar_8, Ar_9, Ar_{10} and Ar_{11} are each independently a 5- to 10-membered aromatic heterocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of said Ar_1, Ar_2, Ar_3, Ar_4, Ar_5, Ar_6, Ar_7, Ar_8, Ar_9, and Ar_{10} being optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, $-C_{1-6}$alkyl, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, and $-NR_{19}R_{20}$; wherein each of said $-C_{1-6}$alkyl is optionally and independently substituted with from 1 to 3 -halo;

Het_1, Het_2, Het_3, Het_4, Het_5, Het_6, Het_7, Het_8, Het_9, Het_{10}, and Het_{12} are each independently a 4- to 10-membered heterocycle having from 1 to 3 heteroatoms selected from O, N and S, wherein each of said Het_1, Het_2, Het_3, Het_4, Het_5, Het_6, Het_7, Het_8, Het_9, Het_{10}, and Het_{12} is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, $-C_{1-}$

$_6$alkyl, -OC_{1-6}alkyl, -SC_{1-6}alkyl, =O, -(C=O)-C_{1-6}alkyl, and -$NR_{21}R_{22}$; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 -halo;

Z_1, Z_2, Z_3, Z_4 and Z_5 are each independently selected from C and N; and

m and n are each independently 1, 2, 3, or 4;

for use in the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease.

Unless indicated otherwise, all of the above radicals can be read both ways. For example, when A is -(C=O)-NR_5-, the -(C=O)- may be attached to X_2 and -NR_5- attached to X_1. Alternatively, the -(C=O)- may be attached to X_1 and -NR_5- attached to X_1. What is called "left part" of a radical is for example when A is -(C=O)-NR_5-, -(C=O)-, and the "right part" is -NR_5-.

Preferably, A is such as the left part of the possible values of A (i.e. in particular –(C=N) from –(C=N)-R_{49}, -(C=O) from -(C=O)-NR_5, -(C=S) from -(C=S)-NR_5, -SO_2 from -SO_2-NR_5-, etc) is attached to X_1. Alternatively, A is such as the right part of the possible values of A (i.e. in particular (R_{49})- from –(C=N)R_{49}, (NR_5)- from -(C=O)-NR_5, -NR_5 from -(C=S)-NR_5, -NR_5-from -SO_2-NR_5-, etc) is attached to X_1.

Preferably, X_1 is such as the left part of the possible values of X_1 (i.e. in particular –O from –O-C_{1-6}alkyl, -S from –S-C_{1-6}alkyl, -NR_3 from -NR_3-(C=O) and -NR_3-C_{1-6}alkyl, -SO_2 from -SO_2-NR_3, etc) is attached to the Z_1-Z_5 aryl or heteroaryl moiety. Alternatively, X_1 is such as the right part of the possible values of X_1 (i.e. in particular (C_{1-6}alkyl)- from –O-C_{1-6}alkyl, –S-C_{1-6}alkyl and -NR_3-C_{1-6}alkyl, -(C=O) from -NR_3-(C=O), (NR_3)- from -SO_2-NR_3, etc) is attached to the Z_1-Z_5 aryl or heteroaryl moiety.

Preferably, X_2 is such as the left part of the possible values of X_2 (i.e. in particular –O from –O-C_{1-6}alkyl, -S from –S-C_{1-6}alkyl, -(C=O) from –(C=O)-NR_2, -NR_2 from -NR_2-C_{1-6}alkyl, -SO_2 from -SO_2-NR_2, etc) is attached to the pyrazolopyrimidine moiety. Alternatively, X_2 is such as the right part of the possible values of X_2 (i.e. in particular (C_{1-6}alkyl)- from –O-C_{1-6}alkyl, –S-C_{1-6}alkyl and -NR_2-C_{1-6}alkyl, (NR_2)- from –(C=O)-NR_2 and -SO_2-NR_2, etc) is attached to the pyrazolopyrimidine moiety. The same principle applies to all the radicals of the invention unless specified otherwise.

When describing the compounds of the invention, the terms used are to be construed in accordance with the following definitions, unless a context dictates otherwise:

The term "alkyl" by itself or as part of another substituent refers to fully saturated hydrocarbon radicals. Generally, alkyl groups of this invention comprise from 1 to 6 carbon atoms. Alkyl groups may be linear or branched and may be substituted as indicated herein. When a subscript is used herein following a carbon atom, the subscript refers to the number of carbon atoms that the named group may contain. Thus, for example, C_{1-6}alkyl means an alkyl of one to six carbon atoms. Examples of alkyl groups are methyl, ethyl, n-propyl, i-propyl, butyl, and its isomers (e.g. n-butyl, i-butyl and t-butyl); pentyl and its isomers, hexyl and its isomers. C_1-C_6 alkyl includes all linear,

branched, or cyclic alkyl groups with between 1 and 6 carbon atoms, and thus includes methyl, ethyl, n-propyl, i-propyl, butyl and its isomers (e.g. n-butyl, i-butyl and t-butyl); pentyl and its isomers, hexyl and its isomers, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

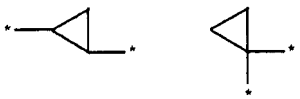
The term "optionally substituted alkyl" refers to an alkyl group optionally substituted with one or more substituents (for example 1 to 3 substituents, for example 1, 2 or 3 substituents or 1 to 2 substituents) at any available point of attachment. Non-limiting examples of such substituents include –halo, -OH, primary and secondary amides, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, heteroaryl, aryl, and the like.

The term "cycloalkyl" by itself or as part of another substituent is a cyclic alkyl group, that is to say, a monovalent, saturated, or unsaturated hydrocarbyl group having a cyclic structure. Cycloalkyl includes all saturated or partially saturated (containing 1 or 2 double bonds) hydrocarbon groups having a cyclic structure. Cycloalkyl groups may comprise 3 or more carbon atoms in the ring and generally, according to this invention comprise from 3 to 6 atoms. Examples of cycloalkyl groups include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

Cycloalkyl as referred herein also includes substituted cycloalkyl groups, wherein such groups may be substituted once or more, and preferably once, twice or thrice. Substituents may be selected from -C_{1-6}alkyl and those defined above for substituted alkyl.

Where alkyl groups as defined are divalent, i.e., with two single bonds for attachment to two other groups, they are termed "alkylene" groups. Non-limiting examples of alkylene groups includes methylene, ethylene, methylmethylene, trimethylene, propylene, tetramethylene, ethylethylene, 1,2-dimethylethylene, pentamethylene and hexamethylene.

Generally, alkylene groups of this invention preferably comprise the same number of carbon atoms as their alkyl counterparts. Where an alkylene or cycloalkylene biradical is present, connectivity to the molecular structure of which it forms part may be through a common carbon atom or different carbon atom. To illustrate this applying the asterisk nomenclature of this invention, a C_3 alkylene group may be for example *-$CH_2CH_2CH_2$-*, *-CH(-CH_2CH_3)-*, or *-CH_2CH(-CH_3)-*. Likewise a C_3 cycloalkylene group may be



The terms "heterocycle" as used herein by itself or as part of another group refer to non-aromatic, fully saturated or partially unsaturated cyclic groups (for example, 3 to 6 membered monocyclic ring systems, or 8-10 membered bicyclic rings) which have at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3 or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms. An optionally substituted heterocyclic refers to a heterocyclic having optionally one or more substituents (for example 1 to 4 substituents, or for example 1, 2, 3 or 4), selected from those defined above for substituted alkyl.

Exemplary heterocyclic groups include piperidinyl, azetidinyl, imidazolinyl, imidazolidinyl, isoxazolinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, piperidyl, succinimidyl, 3H-indolyl, isoindolinyl, chromenyl, isochromanyl, xanthenyl, 2H-pyrrolyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, 4H-quinolizinyl, 4aH-carbazolyl, 2-oxopiperazinyl, piperazinyl, homopiperazinyl, 2-pyrazolinyl, 3-pyrazolinyl, pyranyl, dihydro-2H-pyranyl, 4H-pyranyl, 3,4-dihydro-2H-pyranyl, phthalazinyl, oxetanyl, thietanyl, 3-dioxolanyl, 1,3-dioxanyl, 2,5-dioximidazolidinyl, 2,2,4-piperidonyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, indolinyl, tetrahydropyranyl, tetrahydrofuranyl, tetrehydrothienyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, thiomorpholinyl, thiomorpholinyl sulfoxide, thiomorpholinyl sulfone, 1,3-dioxolanyl, 1,4-oxathianyl, 1,4-dithianyl, 1,3,5-trioxanyl, 6H-1,2,5-thiadiazinyl, 2H-1,5,2-dithiazinyl, 2H-oxocinyl, 1H-pyrrolizinyl, tetrahydro-1,1-dioxothienyl, N- formylpiperazinyl, and morpholinyl; in particular pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, dioxolanyl, dioxanyl, morpholinyl, thiomorpholinyl, piperazinyl, thiazolidinyl, tetrahydropyranyl, and tetrahydrofuranyl.

8-10 membered heterocyclic groups are also meant to include spiro-groups, which are bicyclic compounds with both rings connected through a single atom, such as for example spiro[4.5]decane, which is a spiro compound consisting of a cyclohexane ring and a cyclopentane ring.

The term "aryl" as used herein refers to a polyunsaturated, aromatic hydrocarbyl group having from 5-10 atoms. Aryl is also intended to include the partially hydrogenated derivatives of the carbocyclic systems enumerated herein. Non-limiting examples of aryl comprise phenyl, biphenylyl, biphenylenyl, 5- or 6-tetralinyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, or 8-azulenyl, 1- or 2-naphthyl, 1-, 2-, or 3-indenyl, 1-, 2-, or 9-anthryl, 1- 2-, 3-, 4-, or 5-acenaphtylenyl, 3-, 4-, or 5-acenaphtenyl, 1-, 2-, 3-, 4-, or 10-phenanthryl, 1- or 2-pentalenyl, 1, 2-, 3-, or 4-fluorenyl, 4- or 5-indanyl, 5-, 6-, 7-, or 8-tetrahydronaphthyl, 1,2,3,4-tetrahydronaphthyl, 1,4-dihydronaphthyl, dibenzo[a,d]cylcoheptenyl, and 1-, 2-, 3-, 4-, or 5-pyrenyl; in particular phenyl.

The aryl ring can optionally be substituted by one or more substituents. An "optionally substituted aryl" refers to an aryl having optionally one or more substituents (for example 1 to 5 substituents, for example 1, 2, 3 or 4) at any available point of attachment, selected from those defined above for substituted alkyl.

Where a carbon atom in an aryl group is replaced with a heteroatom, the resultant ring is referred to herein as a heteroaryl ring.

The term "heteroaryl" as used herein by itself or as part of another group refers but is not limited to 5 to 10 carbon-atom aromatic rings in which one or more carbon atoms can be replaced by oxygen, nitrogen or sulfur atoms. Non-limiting examples of such heteroaryl, include: pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, oxatriazolyl, thiatriazolyl, pyridinyl, pyrimidyl, pyrazinyl, pyridazinyl, oxazinyl, dioxinyl, thiazinyl, triazinyl, imidazo[2,1-b][1,3]thiazolyl, thieno[3,2-b]furanyl, thieno[3,2-b]thiophenyl, thieno[2,3-d][1,3]thiazolyl, thieno[2,3-d]imidazolyl, tetrazolo[1,5-a]pyridinyl, indolyl, indolizinyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzothiophenyl, isobenzothiophenyl, indazolyl,

benzimidazolyl, 1,3-benzoxazolyl, 1,2-benzisoxazolyl, 2,1-benzisoxazolyl, 1,3-benzothiazolyl, 1,2-benzoisothiazolyl, 2,1-benzoisothiazolyl, benzotriazolyl, 1,2,3-benzoxadiazolyl, 2,1,3-benzoxadiazolyl, 1,2,3-benzothiadiazolyl, 2,1,3-benzothiadiazolyl, thienopyridinyl, purinyl, imidazo[1,2-a]pyridinyl, 6-oxo-pyridazin-1(6H)-yl, 2-oxopyridin-1(2H)-yl, 6-oxo-pyridazin-1(6H)-yl, 2-oxopyridin-1(2H)-yl, 1,3-benzodioxolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl, 7-azaindolyl, 6-azaindolyl, 5-azaindolyl, 4-azaindolyl.

An "optionally substituted heteroaryl" refers to a heteroaryl having optionally one or more substituents (for example 1 to 4 substituents, for example 1, 2, 3 or 4), selected from those defined above for substituted alkyl.

The term "halo" or "halogen" as a group or part of a group is generic for fluoro, chloro, bromo, or iodo, as well as any suitable isotope thereof.

Whenever the term "substituted" is used in the present invention, it is meant to indicate that one or more hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from the indicated group, provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a chemically stable compound, i.e. a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into a therapeutic and/or diagnostic agent.

Where groups may be optionally substituted, such groups may be substituted once or more, and preferably once, twice or thrice. Substituents may be selected from, those defined above for substituted alkyl.

As used herein the terms such as "alkyl, aryl, or cycloalkyl, each being optionally substituted with" or "alkyl, aryl, or cycloalkyl, optionally substituted with" refers to optionally substituted alkyl, optionally substituted aryl and optionally substituted cycloalkyl.

More generally, from the above, it will be clear to the skilled person that the compounds of the invention may exist in the form of different isomers and/or tautomers, including but not limited to geometrical isomers, conformational isomers, E/Z-isomers, stereochemical isomers (i.e. enantiomers and diastereoisomers) and isomers that correspond to the presence of the same substituents on different positions of the rings present in the compounds of the invention. All such possible isomers, tautomers and mixtures thereof are included within the scope of the invention.

In addition, the invention includes isotopically-labelled compounds and salts, which are identical to compounds of formula (I), but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number most commonly found in nature. Examples of isotopes that can be incorporated into compounds of formula (I) are isotopes of hydrogen, carbon, nitrogen, fluorine, such as ^{3}H, ^{11}C, ^{13}N, ^{14}C, ^{15}O and ^{18}F. Such isotopically-labelled compounds of formula (I) are useful in drug and/or substrate tissue distribution assays. For example ^{11}C and ^{18}F isotopes are particularly useful in PET (Positron Emission Tomography). PET is useful as a diagnostic or treatment follow-up tool that can be applied in a translational manner in a preclinical and clinical setting. It also has applications in PK determination of compounds, including biodistribution. Isotopically labeled compounds of formula (I) can generally

be prepared by carrying out the procedures disclosed below, by substituting a readily available non-isotopically labeled reagent with an isotopically labeled reagent.

Whenever used in the present invention the term "compounds of the invention" or a similar term is meant to include the compounds of general Formula I and any subgroup thereof. This term also refers to the compounds as depicted in Table 1, their derivatives, *N*-oxides, salts, solvates, hydrates, stereoisomeric forms, racemic mixtures, tautomeric forms, optical isomers, analogues, pro-drugs, esters, and metabolites, as well as their quaternized nitrogen analogues. The *N*-oxide forms of said compounds are meant to comprise compounds wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide.

As used in the specification and the appended claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. By way of example, "a compound" means one compound or more than one compound.

The terms described above and others used in the specification are well understood to those in the art.

In a particular embodiment, the present invention provides compounds of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof; for use in the diagnosis prevention and/or treatment of a RIP2-kinase associated disease; wherein one or more of the following applies

A_1 and A_2 are selected from C and N; wherein when A_1 is C, then A_2 is N; and wherein when A_2 is C, then A_1 is N;

R_1 and R_{41} are each independently selected from –H, –halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -NR_9R_{10}, -(C=O)-R_4, -(C=S)-R_4, -SO_2-R_4, -CN, -NR_9-SO_2-R_4, -C_{3-6}cycloalkyl, -Ar_7 and –Het_1; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, -$NR_{11}R_{12}$, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;

R_2 is selected from –H, -halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -(C=O)-C_{1-6}alkyl, -(C=S)-C_{1-6}alkyl, -(C=O)-O-C_{1-6}alkyl, -(C=S)-O-C_{1-6}alkyl, -(C=O)-$NR_{27}R_{28}$, -(C=S)-$NR_{27}R_{28}$, -C_{3-6}cycloalkyl, -Het_3, -Ar_2, -(C=O)-Het_3, -(C=S)-Het_3, -(C=O)-Ar_2, -(C=S)-Ar_2, -(C=O)-C_{3-6}cycloalkyl, -(C=S)-C_{3-6}cycloalkyl, and -SO_2-C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_3, -Ar_2, and -$NR_{13}R_{14}$;

R_3 is selected from –H, -halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -(C=O)-C_{1-6}alkyl, -(C=S)-C_{1-6}alkyl, -(C=O)-O-C_{1-6}alkyl, -(C=S)-O-C_{1-6}alkyl, -(C=O)-$NR_{29}R_{30}$, -(C=S)-$NR_{29}R_{30}$, -C_{3-6}cycloalkyl -Het_2, -Ar_3, -(C=O)-Het_2, -(C=S)-Het_2, -(C=O)-Ar_3, -(C=S)-Ar_3, -(C=O)-C_{3-6}cycloalkyl, -(C=S)-C_{3-6}cycloalkyl and -SO_2-C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Het_2, -Ar_3, and -$NR_{15}R_{16}$;

R_4 is independently selected from –halo, –OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -$NR_{17}R_{18}$, -C_{3-6}cycloalkyl, -Ar_8 and -Het_4;

R_5 and R_7 are each independently selected from –H, -OH, -halo, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_9, -Ar_1, -C_{3-6}cycloalkyl, -SO_2-Ar_1, -SO_2, -SO_2-C_{1-6}alkyl, -(C=O), -(C=O)-C_{1-6}alkyl, -(C=S), -(C=S)-C_{1-6}alkyl, -O-(C=O)-C_{1-6}alkyl, -O-(C=S)-C_{1-6}alkyl, -(C=O)-O-C_{1-6}alkyl, and -(C=S)-O-C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Ar_1, -Het_9, and -$NR_{23}R_{24}$;

R_6 is selected from -C_{1-6}alkyl, -SO_2, -SO_2-C_{1-6}alkyl, -SO_2-C_{3-6}cycloalkyl, -(C=O), -(C=O)-C_{1-6}alkyl, -(C=O)-C_{2-6}alkenyl, -(C=O)-O-C_{1-6}alkyl, -(C=O)-Het_6, -(C=O)-Ar_6, -(C=O)-C_{3-6}cycloalkyl, -(C=O)-$NR_{31}R_{32}$, -(C=O)-NR_{31}-(C=O)-R_{32}, -(C=S), -(C=S)-C_{1-6}alkyl, -(C=S)-C_{2-6}alkenyl, -(C=S)-O-C_{1-6}alkyl, -(C=S)-Het_6, -(C=S)-Ar_6, -(C=S)-C_{3-6}cycloalkyl, -(C=S)-$NR_{31}R_{32}$, -(C=S)-NR_{31}-(C=S)-R_{32}, -Het_6, -Ar_6, and -C_{3-6}cycloalkyl;

wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from =O, –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Het_6, -Ar_6, -$NR_{25}R_{26}$, -(C=O)-$NR_{25}R_{26}$, -NR_{33}(C=O)-$NR_{25}R_{26}$, -(C=S)-$NR_{25}R_{26}$, and -NR_{33}(C=S)-$NR_{25}R_{26}$; and

wherein each of said -C_{3-6}cycloalkyl is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl, =O, –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_{12}, -Ar_{11}, and –$NR_{53}R_{54}$, -(C=O)-$NR_{53}R_{54}$, -NR_{55}(C=O)-$NR_{53}R_{54}$, -(C=S)-$NR_{53}R_{54}$, and -NR_{55}(C=S)-$NR_{53}R_{54}$;

R_8 is selected from –NR_{34}-(C=O)-R_{35}, –NR_{34}-(C=S)-R_{35}, -NR_{36}-(C=O)-$NR_{34}R_{35}$, -NR_{36}-(C=S)-$NR_{34}R_{35}$, -NR_{34}-(SO_2)-R_{35}, -NR_{34}-(C=O)-O-R_{35}, -NR_{34}-(C=S)-O-R_{35}, -O-(C=O)-$NR_{34}R_{35}$, and -O-(C=S)-$NR_{34}R_{35}$;

R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, R_{29}, R_{30}, R_{31}, R_{32}, R_{33}, R_{34}, R_{35}, R_{36}, R_{37}, R_{38}, R_{39}, R_{40}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, R_{49}, R_{50}, R_{53}, R_{54} and R_{55} are each independently selected from –H, -halo, =O, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Ar_5 and –Het_7; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Het_7, -Ar_5 and –$NR_{51}R_{52}$;

R_{51} and R_{52} are each independently selected from –H, -halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Ar_{10} and –Het_{10};

R_{42} is selected from -H, -OH, -halo, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -$NR_{46}R_{47}$, -C_{3-6}cycloalkyl, -Ar_9 and -Het_8;

R_{43} is selected from –H -C_{1-6}alkyl, and -C_{3-6}cycloalkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_5, -C_{3-6}cycloalkyl –Ar_4, and –$NR_{44}R_{45}$;

A is selected from -$(CH_2)_n$-Y-$(CH_2)_m$-, –(C=O)-, –(C=S)-, -(C=N)-R_{49}-, -(SO_2)-, -SO_2-NR_5-, -(C=O)-NR_5-, -(C=S)-NR_5-, -NR_5-(C=O)-NR_7-, -NR_5-(C=S)-NR_7-, -NR_6,-, -NR_5-(C=O)-O-, -NR_5-(C=S)-O-, and -CHR_8- ;

X_1 is selected from –C_{1-6}alkyl-, –O-C_{1-6}alkyl-, –S-C_{1-6}alkyl-, -(C=O)-, -NR_3-(C=O)-, -C_{1-6}alkyl-NR_3-, -NR_3-, -(C=O)-, -NR_3-(C=O)-NR_{48}-, -NR_3-C_{1-6}alkyl-, -NR_3-SO_2-, -NR_3-(C=O)-C_{1-6}alkyl-, -(C=O)-

NR_3-C_{1-6}alkyl-, –O-C_{1-6}alkyl-O-C_{1-6}alkyl- and -C_{1-6}alkyl-NR_3-C_{1-6}alkyl-; wherein each of said -C_{1-6}alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -phenyl, and -$NR_{37}R_{38}$;

X_2 is selected from –C_{1-6}alkyl-, –O-C_{1-6}alkyl-, –S-C_{1-6}alkyl-, -(C=O)-, -NR_2-(C=O)-, -C_{1-6}alkyl-NR_2-, -NR_2-, -(C=O)-, -NR_2-(C=O)-NR_{50}-, -NR_2-C_{1-6}alkyl-, -NR_2-SO_2-, -NR_2-(C=O)-C_{1-6}alkyl-, -(C=O)-NR_2-C_{1-6}alkyl-, –O-C_{1-6}alkyl-O-C_{1-6}alkyl- and -C_{1-6}alkyl-NR_2-C_{1-6}alkyl-; wherein each of said -C_{1-6}alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -phenyl and -$NR_{39}R_{40}$;

Y is selected from a direct bond, -CHR_{42}-, -O-, -S-, and –NR_{43}-;

Ar_1, Ar_2, Ar_3, Ar_4, Ar_5, Ar_6, Ar_7, Ar_8, Ar_9, Ar_{10} and Ar_{11} are each independently a 5- to 10-membered aromatic heterocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of said Ar_1, Ar_2, Ar_3, Ar_4, Ar_5, Ar_6, Ar_7, Ar_8, Ar_9, and Ar_{10} being optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, and –$NR_{19}R_{20}$; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 -halo;

Het_1, Het_2, Het_3, Het_4, Het_5, Het_6, Het_7, Het_8, Het_9, Het_{10}, and Het_{12} are each independently a 4- to 10-membered heterocycle having from 1 to 3 heteroatoms selected from O, N and S, wherein each of said Het_1, Het_2, Het_3, Het_4, Het_5, Het_6, Het_7, Het_8, Het_9, Het_{10}, and Het_{12} is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, –C_{1-6}alkyl, -OC_{1-6}alkyl, -SC_{1-6}alkyl, =O, -(C=O)-C_{1-6}alkyl, and -$NR_{21}R_{22}$; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 -halo;

Z_1, Z_2, Z_3, Z_4 and Z_5 are each independently selected from C and N; and

m and n are each independently 1, 2, 3, or 4;

In particular, X_1, and X_2 as used herein, represent biradicals, which taken together with the radicals to which they are attached form a macrocyclic pyrazolopyrimidine compound. Said biradicals may be present in either of both directions in the macrocyclic pyrazolopyrimidine, but are preferably present in the direction as described below:

Referring to formula I:

X_1 is selected from the list comprising *–C_{1-6}alkyl-, *–O-C_{1-6}alkyl-, *–S-C_{1-6}alkyl-, *-(C=O)-, -NR_3-(C=O)-, *-C_{1-6}alkyl-NR_3-, *-NR_3-, *-(C=O)-, *-NR_3-(C=O)-NR_{48}-, *-NR_3-C_{1-6}alkyl-, *-NR_3-SO_2-, *-NR_3-(C=O)-C_{1-6}alkyl-, *-(C=O)-NR_3-C_{1-6}alkyl-, *–O-C_{1-6}alkyl-O-C_{1-6}alkyl- and *-C_{1-6}alkyl-NR_3-C_{1-6}alkyl-; wherein said biradical is preferably attached to the aryl or heteroaryl moiety via *;

X_2 is selected from the list comprising *–C_{1-6}alkyl-, *–O-C_{1-6}alkyl-, *–S-C_{1-6}alkyl-, *-(C=O)-, *-NR_2-(C=O)-, *-C_{1-6}alkyl-NR_2-, *-NR_2-, *-(C=O)-, *-NR_2-(C=O)-NR_{50}-, *-NR_2-C_{1-6}alkyl-, *-NR_2-SO_2-, *-NR_2-(C=O)-C_{1-6}alkyl-, *-(C=O)-NR_2-C_{1-6}alkyl-, *–O-C_{1-6}alkyl-O-C_{1-6}alkyl- and *-C_{1-6}alkyl-NR_2-C_{1-6}alkyl-; wherein said biradical is preferably attached to the pyrazolopyrimidine moiety via *;

In a preferred embodiment, the present invention provides compounds of formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, for use in the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease wherein

A_1 is C and A_2 is N;

R_1 and R_{41} are each independently selected from –H, –halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -NR_9R_{10}, -(C=O)-R_4, -(C=S)-R_4, -SO_2-R_4, -CN, -NR_9-SO_2-R_4, -C_{3-6}cycloalkyl, -Ar_7 and –Het_1; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, -$NR_{11}R_{12}$, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;

R_2 is selected from –H, -halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -(C=O)-C_{1-6}alkyl, -(C=S)-C_{1-6}alkyl, -(C=O)-O-C_{1-6}alkyl, -(C=S)-O-C_{1-6}alkyl, -(C=O)-$NR_{27}R_{28}$, -(C=S)-$NR_{27}R_{28}$, -C_{3-6}cycloalkyl, -Het_3, -Ar_2, -(C=O)-Het_3, -(C=S)-Het_3, -(C=O)-Ar_2, -(C=S)-Ar_2, -(C=O)-C_{3-6}cycloalkyl, -(C=S)-C_{3-6}cycloalkyl, and -SO_2-C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_3, -Ar_2, and -$NR_{13}R_{14}$;

R_3 is selected from –H, -halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -(C=O)-C_{1-6}alkyl, -(C=S)-C_{1-6}alkyl, -(C=O)-O-C_{1-6}alkyl, -(C=S)-O-C_{1-6}alkyl, -(C=O)-$NR_{29}R_{30}$, -(C=S)-$NR_{29}R_{30}$, -C_{3-6}cycloalkyl -Het_2, -Ar_3, -(C=O)-Het_2, -(C=S)-Het_2, -(C=O)-Ar_3, -(C=S)-Ar_3, -(C=O)-C_{3-6}cycloalkyl, -(C=S)-C_{3-6}cycloalkyl and -SO_2-C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Het_2, -Ar_3, and -$NR_{15}R_{16}$;

R_4 is independently selected from –halo, –OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -$NR_{17}R_{18}$, -C_{3-6}cycloalkyl, -Ar_8 and -Het_4;

R_5 and R_7 are each independently selected from –H, -OH, -halo, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_9, -Ar_1, -C_{3-6}cycloalkyl, -SO_2-Ar_1, -SO_2, -SO_2-C_{1-6}alkyl, -(C=O), -(C=O)-C_{1-6}alkyl, -(C=S), -(C=S)-C_{1-6}alkyl, -O-(C=O)-C_{1-6}alkyl, -O-(C=S)-C_{1-6}alkyl, -(C=O)-O-C_{1-6}alkyl, and -(C=S)-O-C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Ar_1, -Het_9, and -$NR_{23}R_{24}$;

R_6 is selected from -C_{1-6}alkyl, -SO_2, -SO_2-C_{1-6}alkyl, -SO_2-C_{3-6}cycloalkyl, -(C=O), -(C=O)-C_{1-6}alkyl, -(C=O)-C_{2-6}alkenyl, -(C=O)-O-C_{1-6}alkyl, -(C=O)-Het_6, -(C=O)-Ar_6, -(C=O)-C_{3-6}cycloalkyl, -(C=O)-$NR_{31}R_{32}$, -(C=O)-NR_{31}-(C=O)-R_{32}, -(C=S), -(C=S)-C_{1-6}alkyl, -(C=S)-C_{2-6}alkenyl, -(C=S)-O-C_{1-6}alkyl, -(C=S)-Het_6, -(C=S)-Ar_6, -(C=S)-C_{3-6}cycloalkyl, -(C=S)-$NR_{31}R_{32}$, -(C=S)-NR_{31}-(C=S)-R_{32}, -Het_6, -Ar_6, and -C_{3-6}cycloalkyl;

wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from =O, –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Het_6, -Ar_6, -$NR_{25}R_{26}$, -(C=O)-$NR_{25}R_{26}$, -NR_{33}(C=O)-$NR_{25}R_{26}$, -(C=S)-$NR_{25}R_{26}$, and -NR_{33}(C=S)-$NR_{25}R_{26}$; and

wherein each of said -C_{3-6}cycloalkyl is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl, =O, –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_{12}, -Ar_{11},

and $-NR_{53}R_{54}$, $-(C=O)-NR_{53}R_{54}$, $-NR_{55}(C=O)-NR_{53}R_{54}$, $-(C=S)-NR_{53}R_{54}$, and $-NR_{55}(C=S)-NR_{53}R_{54}$;

R_8 is selected from $-NR_{34}-(C=O)-R_{35}$, $-NR_{34}-(C=S)-R_{35}$, $-NR_{36}-(C=O)-NR_{34}R_{35}$, $-NR_{36}-(C=S)-NR_{34}R_{35}$, $-NR_{34}-(SO_2)-R_{35}$, $-NR_{34}-(C=O)-O-R_{35}$, $-NR_{34}-(C=S)-O-R_{35}$, $-O-(C=O)-NR_{34}R_{35}$, and $-O-(C=S)-NR_{34}R_{35}$;

R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, R_{29}, R_{30}, R_{31}, R_{32}, R_{33}, R_{34}, R_{35}, R_{36}, R_{37}, R_{38}, R_{39}, R_{40}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, R_{49}, R_{50}, R_{53}, R_{54} and R_{55} are each independently selected from –H, -halo, =O, -OH, $-C_{1-6}$alkyl, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-C_{3-6}$cycloalkyl, $-Ar_5$ and $-Het_7$; wherein each of said $-C_{1-6}$alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-C_{3-6}$cycloalkyl, $-Het_7$, $-Ar_5$ and $-NR_{51}R_{52}$;

R_{51} and R_{52} are each independently selected from –H, -halo, -OH, $-C_{1-6}$alkyl, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-C_{3-6}$cycloalkyl, $-Ar_{10}$ and $-Het_{10}$;

R_{42} is selected from -H, -OH, -halo, $-C_{1-6}$alkyl, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-NR_{46}R_{47}$, $-C_{3-6}$cycloalkyl, $-Ar_9$ and $-Het_8$;

R_{43} is selected from –H $-C_{1-6}$alkyl, and $-C_{3-6}$cycloalkyl; wherein each of said $-C_{1-6}$alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-Het_5$, $-C_{3-6}$cycloalkyl $-Ar_4$, and $-NR_{44}R_{45}$;

A is selected from $-(CH_2)_n-Y-(CH_2)_m-$, –(C=O)-, –(C=S)-, -(C=N)-R_{49}-, $-(SO_2)-$, $-SO_2-NR_5-$, $-(C=O)-NR_5-$, $-(C=S)-NR_5-$, $-NR_5-(C=O)-NR_7-$, $-NR_5-(C=S)-NR_7-$, $-NR_6-$, $-NR_5-(C=O)-O-$, $-NR_5-(C=S)-O-$, and $-CHR_8-$;

X_1 is selected from $-C_{1-6}$alkyl-, $-O-C_{1-6}$alkyl-, $-S-C_{1-6}$alkyl-, -(C=O)-, $-NR_3-(C=O)-$, $-C_{1-6}$alkyl-NR_3-, $-NR_3-$, -(C=O)-, $-NR_3-(C=O)-NR_{48}-$, $-NR_3-C_{1-6}$alkyl-, $-NR_3-SO_2-$, $-NR_3-(C=O)-C_{1-6}$alkyl-, $-(C=O)-NR_3-C_{1-6}$alkyl-, $-O-C_{1-6}$alkyl-O-C_{1-6}alkyl- and $-C_{1-6}$alkyl-NR_3-C_{1-6}alkyl-; wherein each of said $-C_{1-6}$alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, $-C_{1-6}$alkyl, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, -phenyl, and $-NR_{37}R_{38}$;

X_2 is selected from $-C_{1-6}$alkyl-, $-O-C_{1-6}$alkyl-, $-S-C_{1-6}$alkyl-, -(C=O)-, $-NR_2-(C=O)-$, $-C_{1-6}$alkyl-NR_2-, $-NR_2-$, -(C=O)-, $-NR_2-(C=O)-NR_{50}-$, $-NR_2-C_{1-6}$alkyl-, $-NR_2-SO_2-$, $-NR_2-(C=O)-C_{1-6}$alkyl-, $-(C=O)-NR_2-C_{1-6}$alkyl-, $-O-C_{1-6}$alkyl-O-C_{1-6}alkyl- and $-C_{1-6}$alkyl-NR_2-C_{1-6}alkyl-; wherein each of said $-C_{1-6}$alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, $-C_{1-6}$alkyl, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, -phenyl and $-NR_{39}R_{40}$;

Y is selected from a direct bond, $-CHR_{42}-$, -O-, -S-, and $-NR_{43}-$;

Ar_1, Ar_2, Ar_3, Ar_4, Ar_5, Ar_6, Ar_7, Ar_8, Ar_9, Ar_{10} and Ar_{11} are each independently a 5- to 10-membered aromatic heterocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of said Ar_1, Ar_2, Ar_3, Ar_4, Ar_5, Ar_6, Ar_7, Ar_8, Ar_9, and Ar_{10} being optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, $-C_{1-6}$alkyl, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, and $-NR_{19}R_{20}$; wherein each of said $-C_{1-6}$alkyl is optionally and independently substituted with from 1 to 3 -halo;

Het_1, Het_2, Het_3, Het_4, Het_5, Het_6, Het_7, Het_8, Het_9, Het_{10}, and Het_{12} are each independently a 4- to 10-membered heterocycle having from 1 to 3 heteroatoms selected from O, N and S, wherein

each of said Het_1, Het_2, Het_3, Het_4, Het_5, Het_6, Het_7, Het_8, Het_9, Het_{10}, and Het_{12} is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, $-C_{1-6}$alkyl, $-OC_{1-6}$alkyl, $-SC_{1-6}$alkyl, =O, $-(C=O)-C_{1-6}$alkyl, and $-NR_{21}R_{22}$; wherein each of said $-C_{1-6}$alkyl is optionally and independently substituted with from 1 to 3 -halo;

Z_1, Z_2, Z_3, Z_4 and Z_5 are each independently selected from C and N; and

m and n are each independently 1, 2, 3, or 4;

for use in the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease.

In a further embodiment, the present invention provides a compound of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, for use in the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease wherein

A_1 is N and A_2 is C

R_1 and R_{41} are each independently selected from –H, –halo, -OH, $-C_{1-6}$alkyl, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-NR_9R_{10}$, $-(C=O)-R_4$, $-(C=S)-R_4$, $-SO_2-R_4$, -CN, $-NR_9-SO_2-R_4$, $-C_{3-6}$cycloalkyl, $-Ar_7$ and $-Het_1$; wherein each of said $-C_{1-6}$alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, $-NR_{11}R_{12}$, $-O-C_{1-6}$alkyl, and $-S-C_{1-6}$alkyl;

R_2 is selected from –H, -halo, -OH, $-C_{1-6}$alkyl, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-(C=O)-C_{1-6}$alkyl, $-(C=S)-C_{1-6}$alkyl, $-(C=O)-O-C_{1-6}$alkyl, $-(C=S)-O-C_{1-6}$alkyl, $-(C=O)-NR_{27}R_{28}$, $-(C=S)-NR_{27}R_{28}$, $-C_{3-6}$cycloalkyl, $-Het_3$, $-Ar_2$, $-(C=O)-Het_3$, $-(C=S)-Het_3$, $-(C=O)-Ar_2$, $-(C=S)-Ar_2$, $-(C=O)-C_{3-6}$cycloalkyl, $-(C=S)-C_{3-6}$cycloalkyl, and $-SO_2-C_{1-6}$alkyl; wherein each of said $-C_{1-6}$alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-Het_3$, $-Ar_2$, and $-NR_{13}R_{14}$;

R_3 is selected from –H, -halo, -OH, $-C_{1-6}$alkyl, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-(C=O)-C_{1-6}$alkyl, $-(C=S)-C_{1-6}$alkyl, $-(C=O)-O-C_{1-6}$alkyl, $-(C=S)-O-C_{1-6}$alkyl, $-(C=O)-NR_{29}R_{30}$, $-(C=S)-NR_{29}R_{30}$, $-C_{3-6}$cycloalkyl $-Het_2$, $-Ar_3$, $-(C=O)-Het_2$, $-(C=S)-Het_2$, $-(C=O)-Ar_3$, $-(C=S)-Ar_3$, $-(C=O)-C_{3-6}$cycloalkyl, $-(C=S)-C_{3-6}$cycloalkyl and $-SO_2-C_{1-6}$alkyl; wherein each of said $-C_{1-6}$alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-C_{3-6}$cycloalkyl, $-Het_2$, $-Ar_3$, and $-NR_{15}R_{16}$;

R_4 is independently selected from –halo, –OH, $-C_{1-6}$alkyl, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-NR_{17}R_{18}$, $-C_{3-6}$cycloalkyl, $-Ar_8$ and $-Het_4$;

R_5 and R_7 are each independently selected from –H, -OH, -halo, $-C_{1-6}$alkyl, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-Het_9$, $-Ar_1$, $-C_{3-6}$cycloalkyl, $-SO_2-Ar_1$, $-SO_2$, $-SO_2-C_{1-6}$alkyl, -(C=O), $-(C=O)-C_{1-6}$alkyl, -(C=S), $-(C=S)-C_{1-6}$alkyl, $-O-(C=O)-C_{1-6}$alkyl, $-O-(C=S)-C_{1-6}$alkyl, $-(C=O)-O-C_{1-6}$alkyl, and $-(C=S)-O-C_{1-6}$alkyl; wherein each of said $-C_{1-6}$alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-C_{3-6}$cycloalkyl, $-Ar_1$, $-Het_9$, and $-NR_{23}R_{24}$;

R_6 is selected from $-C_{1-6}$alkyl, $-SO_2$, $-SO_2-C_{1-6}$alkyl, $-SO_2-C_{3-6}$cycloalkyl, -(C=O), $-(C=O)-C_{1-6}$alkyl, $-(C=O)-C_{2-6}$alkenyl, $-(C=O)-O-C_{1-6}$alkyl, $-(C=O)-Het_6$, $-(C=O)-Ar_6$, $-(C=O)-C_{3-6}$cycloalkyl, $-(C=O)-NR_{31}R_{32}$, $-(C=O)-NR_{31}-(C=O)-R_{32}$, -(C=S), $-(C=S)-C_{1-6}$alkyl, $-(C=S)-C_{2-6}$alkenyl, $-(C=S)-O-C_{1-}$

$_6$alkyl, -(C=S)-Het$_6$, -(C=S)-Ar$_6$, -(C=S)-C$_{3-6}$cycloalkyl, -(C=S)-NR$_{31}$R$_{32}$, -(C=S)-NR$_{31}$-(C=S)-R$_{32}$, -Het$_6$, -Ar$_6$, and -C$_{3-6}$cycloalkyl;

wherein each of said -C$_{1-6}$alkyl is optionally and independently substituted with from 1 to 3 substituents selected from =O, –halo, –OH, -O-C$_{1-6}$alkyl, -S-C$_{1-6}$alkyl, -C$_{3-6}$cycloalkyl, -Het$_6$, -Ar$_6$, -NR$_{25}$R$_{26}$, -(C=O)-NR$_{25}$R$_{26}$, -NR$_{33}$(C=O)-NR$_{25}$R$_{26}$, -(C=S)-NR$_{25}$R$_{26}$, and -NR$_{33}$(C=S)-NR$_{25}$R$_{26}$; and

wherein each of said -C$_{3-6}$cycloalkyl is optionally and independently substituted with from 1 to 3 substituents selected from -C$_{1-6}$alkyl, =O, –halo, –OH, -O-C$_{1-6}$alkyl, -S-C$_{1-6}$alkyl, -Het$_{12}$, -Ar$_{11}$, and –NR$_{53}$R$_{54}$, -(C=O)-NR$_{53}$R$_{54}$, -NR$_{55}$(C=O)-NR$_{53}$R$_{54}$, -(C=S)-NR$_{53}$R$_{54}$, and -NR$_{55}$(C=S)-NR$_{53}$R$_{54}$;

R$_8$ is selected from –NR$_{34}$-(C=O)-R$_{35}$, –NR$_{34}$-(C=S)-R$_{35}$, -NR$_{36}$-(C=O)-NR$_{34}$R$_{35}$, -NR$_{36}$-(C=S)-NR$_{34}$R$_{35}$, -NR$_{34}$-(SO$_2$)-R$_{35}$, -NR$_{34}$-(C=O)-O-R$_{35}$, -NR$_{34}$-(C=S)-O-R$_{35}$, -O-(C=O)-NR$_{34}$R$_{35}$, and -O-(C=S)-NR$_{34}$R$_{35}$;

R$_9$, R$_{10}$, R$_{11}$, R$_{12}$, R$_{13}$, R$_{14}$, R$_{15}$, R$_{16}$, R$_{17}$, R$_{18}$, R$_{19}$, R$_{20}$, R$_{21}$, R$_{22}$, R$_{23}$, R$_{24}$, R$_{25}$, R$_{26}$, R$_{27}$, R$_{28}$, R$_{29}$, R$_{30}$, R$_{31}$, R$_{32}$, R$_{33}$, R$_{34}$, R$_{35}$, R$_{36}$, R$_{37}$, R$_{38}$, R$_{39}$, R$_{40}$, R$_{44}$, R$_{45}$, R$_{46}$, R$_{47}$, R$_{48}$, R$_{49}$, R$_{50}$, R$_{53}$, R$_{54}$ and R$_{55}$ are each independently selected from –H, -halo, =O, -OH, -C$_{1-6}$alkyl, -O-C$_{1-6}$alkyl, -S-C$_{1-6}$alkyl, -C$_{3-6}$cycloalkyl, -Ar$_5$ and –Het$_7$; wherein each of said -C$_{1-6}$alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C$_{1-6}$alkyl, -S-C$_{1-6}$alkyl, -C$_{3-6}$cycloalkyl, -Het$_7$, -Ar$_5$ and –NR$_{51}$R$_{52}$;

R$_{51}$ and R$_{52}$ are each independently selected from –H, -halo, -OH, -C$_{1-6}$alkyl, -O-C$_{1-6}$alkyl, -S-C$_{1-6}$alkyl, -C$_{3-6}$cycloalkyl, -Ar$_{10}$ and –Het$_{10}$;

R$_{42}$ is selected from -H, -OH, -halo, -C$_{1-6}$alkyl, -O-C$_{1-6}$alkyl, -S-C$_{1-6}$alkyl, -NR$_{46}$R$_{47}$, -C$_{3-6}$cycloalkyl, -Ar$_9$ and -Het$_8$;

R$_{43}$ is selected from –H -C$_{1-6}$alkyl, and -C$_{3-6}$cycloalkyl; wherein each of said -C$_{1-6}$alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C$_{1-6}$alkyl, -S-C$_{1-6}$alkyl, -Het$_5$, -C$_{3-6}$cycloalkyl –Ar$_4$, and –NR$_{44}$R$_{45}$;

A is selected from -(CH$_2$)$_n$-Y-(CH$_2$)$_m$-, –(C=O)-, –(C=S)-, -(C=N)-R$_{49}$-, -(SO$_2$)-, -SO$_2$-NR$_5$-, -(C=O)-NR$_5$-, -(C=S)-NR$_5$-, -NR$_5$-(C=O)-NR$_7$-, -NR$_5$-(C=S)-NR$_7$-, -NR$_6$,-, -NR$_5$-(C=O)-O-, -NR$_5$-(C=S)-O-, and -CHR$_8$- ;

X$_1$ is selected from –C$_{1-6}$alkyl-, –O-C$_{1-6}$alkyl-, –S-C$_{1-6}$alkyl-, -(C=O)-, -NR$_3$-(C=O)-, -C$_{1-6}$alkyl-NR$_3$-, -NR$_3$-, -(C=O)-, -NR$_3$-(C=O)-NR$_{48}$-, -NR$_3$-C$_{1-6}$alkyl-, -NR$_3$-SO$_2$-, -NR$_3$-(C=O)-C$_{1-6}$alkyl-, -(C=O)-NR$_3$-C$_{1-6}$alkyl-, –O-C$_{1-6}$alkyl-O-C$_{1-6}$alkyl- and -C$_{1-6}$alkyl-NR$_3$-C$_{1-6}$alkyl-; wherein each of said -C$_{1-6}$alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, -C$_{1-6}$alkyl, -O-C$_{1-6}$alkyl, -S-C$_{1-6}$alkyl, -phenyl, and -NR$_{37}$R$_{38}$;

X$_2$ is selected from –C$_{1-6}$alkyl-, –O-C$_{1-6}$alkyl-, –S-C$_{1-6}$alkyl-, -(C=O)-, -NR$_2$-(C=O)-, -C$_{1-6}$alkyl-NR$_2$-, -NR$_2$-, -(C=O)-, -NR$_2$-(C=O)-NR$_{50}$-, -NR$_2$-C$_{1-6}$alkyl-, -NR$_2$-SO$_2$-, -NR$_2$-(C=O)-C$_{1-6}$alkyl-, -(C=O)-NR$_2$-C$_{1-6}$alkyl-, –O-C$_{1-6}$alkyl-O-C$_{1-6}$alkyl- and -C$_{1-6}$alkyl-NR$_2$-C$_{1-6}$alkyl-; wherein each of said -C$_{1-6}$alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, -C$_{1-6}$alkyl, -O-C$_{1-6}$alkyl, -S-C$_{1-6}$alkyl, -phenyl and -NR$_{39}$R$_{40}$;

Y is selected from a direct bond, -CHR$_{42}$-, -O-, -S-, and –NR$_{43}$-;

Ar_1, Ar_2, Ar_3, Ar_4, Ar_5, Ar_6, Ar_7, Ar_8, Ar_9, Ar_{10} and Ar_{11} are each independently a 5- to 10-membered aromatic heterocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of said Ar_1, Ar_2, Ar_3, Ar_4, Ar_5, Ar_6, Ar_7, Ar_8, Ar_9, and Ar_{10} being optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, and –$NR_{19}R_{20}$; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 -halo;

Het_1, Het_2, Het_3, Het_4, Het_5, Het_6, Het_7, Het_8, Het_9, Het_{10}, and Het_{12} are each independently a 4- to 10-membered heterocycle having from 1 to 3 heteroatoms selected from O, N and S, wherein each of said Het_1, Het_2, Het_3, Het_4, Het_5, Het_6, Het_7, Het_8, Het_9, Het_{10}, and Het_{12} is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, –C_{1-6}alkyl, -OC_{1-6}alkyl, -SC_{1-6}alkyl, =O, -(C=O)-C_{1-6}alkyl, and -$NR_{21}R_{22}$; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 -halo;

Z_1, Z_2, Z_3, Z_4 and Z_5 are each independently selected from C and N; and

m and n are each independently 1, 2, 3, or 4.

In a further embodiment, the present invention provides a compound of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, for use in the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease wherein

A_1 and A_2 are selected from C and N; wherein when A_1 is C, then A_2 is N; and wherein when A_2 is C, then A_1 is N;

R_1 and R_{41} are each independently selected from –H, –halo, -C_{1-6}alkyl, -(C=O)-R_4, and -CN; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -O-C_{1-6}alkyl;

R_2 is selected from –H, and -C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with -$NR_{13}R_{14}$;

R_3 is selected from –H, and -C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with -$NR_{15}R_{16}$;

R_4 is -$NR_{17}R_{18}$;

R_5 is –H;

R_6 is selected from -C_{1-6}alkyl, -(C=O)-C_{1-6}alkyl, -(C=O)-C_{3-6}cycloalkyl, -Het_6, and -C_{3-6}cycloalkyl;

wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -O-C_{1-6}alkyl and -Het_6;

and wherein each of said -C_{3-6}cycloalkyl is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl;

R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, are each independently selected from –H, and -C_{1-6}alkyl;

R_{43} is selected from –H, and -C_{1-6}alkyl;

A is selected from -$(CH_2)_n$-Y-$(CH_2)_m$-, and -NR_6-, -(C=O)-NR_5- ;

X_1 is selected from –O-C_{1-6}alkyl-, -C_{1-6}alkyl-NR_3-, and -C_{1-6}alkyl-NR_3-C_{1-6}alkyl-; wherein each of said -C_{1-6}alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl;

X_2 is selected from –O-C_{1-6}alkyl-, -C_{1-6}alkyl-NR_2-; wherein each of said -C_{1-6}alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl;

Y is –NR_{43}-;

Het_6 is a 4- to 10-membered heterocycle having from 1 to 3 heteroatoms selected from O, N and S;

Z_1, Z_2, Z_3, Z_4 and Z_5 are each independently selected from C and N; and

m and n are each independently 1, 2, 3, or 4;

In a further embodiment, the present invention provides a compound of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, for use in the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease wherein

A_1 is C and A_2 is N;

R_1 and R_{41} are each independently selected from –H, –halo, -C_{1-6}alkyl, -(C=O)-R_4, and -CN; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -O-C_{1-6}alkyl;

R_2 is selected from –H, and -C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with -$NR_{13}R_{14}$;

R_3 is selected from –H, and -C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with -$NR_{15}R_{16}$;

R_4 is -$NR_{17}R_{18}$;

R_5 is –H;

R_6 is selected from -C_{1-6}alkyl, -(C=O)-C_{1-6}alkyl, -(C=O)-C_{3-6}cycloalkyl, -Het_6, and -C_{3-6}cycloalkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -O-C_{1-6}alkyl and -Het_6;

and wherein each of said -C_{3-6}cycloalkyl is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl;

R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, are each independently selected from –H, and -C_{1-6}alkyl;

R_{43} is selected from –H, and -C_{1-6}alkyl;

A is selected from -$(CH_2)_n$-Y-$(CH_2)_m$-, and -NR_6-, -(C=O)-NR_5- ;

X_1 is selected from –O-C_{1-6}alkyl-, -C_{1-6}alkyl-NR_3-, and -C_{1-6}alkyl-NR_3-C_{1-6}alkyl-; wherein each of said -C_{1-6}alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl;

X_2 is selected from –O-C_{1-6}alkyl-, -C_{1-6}alkyl-NR_2-; wherein each of said -C_{1-6}alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl;

Y is –NR_{43}-;

Het_6 is a 4- to 10-membered heterocycle having from 1 to 3 heteroatoms selected from O, N and S;

Z_1, Z_2, Z_3, Z_4 and Z_5 are each independently selected from C and N; and

m and n are each independently 1, 2, 3, or 4

In a further embodiment, the present invention provides a compound of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, for use in the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease wherein

A_1 is N and A_2 is C;

R_1 and R_{41} are each independently selected from –H, –halo, -C_{1-6}alkyl, -(C=O)-R_4, and -CN; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -O-C_{1-6}alkyl;

R_2 is selected from –H, and -C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with -$NR_{13}R_{14}$;

R_3 is selected from –H, and -C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with -$NR_{15}R_{16}$;

R_4 is -$NR_{17}R_{18}$;

R_5 is –H;

R_6 is selected from -C_{1-6}alkyl, -(C=O)-C_{1-6}alkyl, -(C=O)-C_{3-6}cycloalkyl, -Het_6, and -C_{3-6}cycloalkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -O-C_{1-6}alkyl and -Het_6;

and wherein each of said -C_{3-6}cycloalkyl is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl;

R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, are each independently selected from –H, and -C_{1-6}alkyl;

R_{43} is selected from –H, and -C_{1-6}alkyl;

A is selected from -$(CH_2)_n$-Y-$(CH_2)_m$-, -NR_6-, and -(C=O)-NR_5- ;

X_1 is selected from –O-C_{1-6}alkyl-, -C_{1-6}alkyl-NR_3-, and -C_{1-6}alkyl-NR_3-C_{1-6}alkyl-; wherein each of said -C_{1-6}alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl;

X_2 is selected from –O-C_{1-6}alkyl-, -C_{1-6}alkyl-NR_2-; wherein each of said -C_{1-6}alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl;

Y is –NR_{43}-;

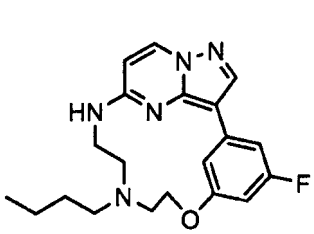
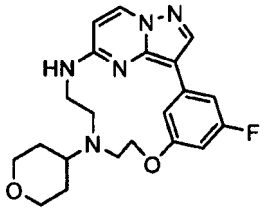
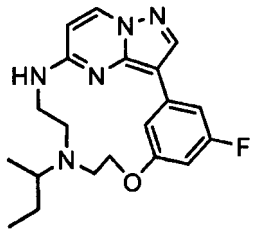
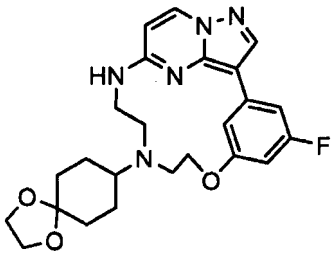
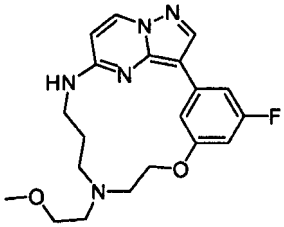
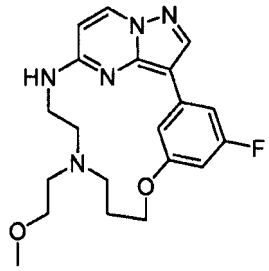
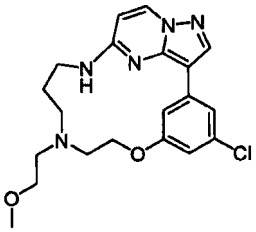
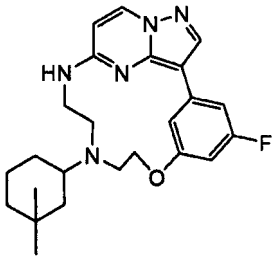
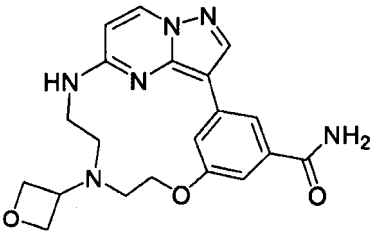
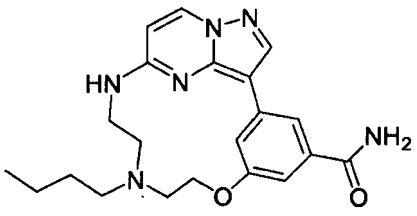
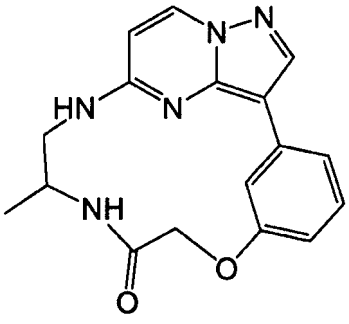
Het_6 is a 4- to 10-membered heterocycle having from 1 to 3 heteroatoms selected from O, N and S;

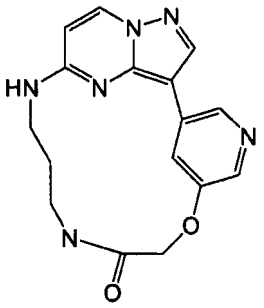
Z_1, Z_2, Z_3, Z_4 and Z_5 are each independently selected from C and N; and

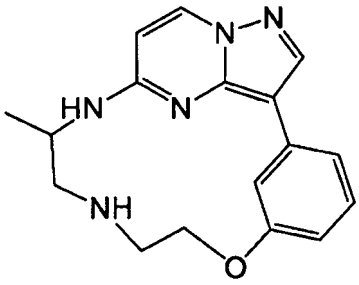
m and n are each independently 1, 2, 3, or 4

In particular in the compounds according to this invention, the pyrazolopyrimidine or the imidazopyridazine moiety is linked to the aryl or heteroaryl moiety at position Z_4 or Z_5, in accordance with the numbering as provided in Formula I. Furthermore, the R_1 of the compounds according to this invention is preferably linked to the aryl or heteroaryl moiety at position Z_1, Z_2 or Z_3, in accordance with the numbering as provided in Formula I.

In yet a further aspect, the present invention provides a compound selected from the list comprising:





The compounds of the present invention can be prepared according to the reaction schemes provided in the examples hereinafter, but those skilled in the art will appreciate that these are only illustrative for the invention and that the compounds of this invention can be prepared by any of several standard synthetic processes commonly used by those skilled in the art of organic chemistry.

METHOD OF TREATMENT

Compounds of formula (I) a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, are inhibitors of RIP2 kinase activity and are thus believed to be of potential use in the diagnosis, prevention and/or treatment of inflammatory disorders, in particular Crohn's disease, bowel disease, Sarcoidosis, psoriasis, rheumatoid arthritis, asthma, ulcerative colitis, lupus, uveitis, blau syndrome, granulomatous inflammation, in particular behçet's disease, multiple sclerosis and insulin-resistant type 2 diabetes.

As used herein, the terms "inflammatory disorder" or "inflammatory disease" can refer to a disorder or disease characterized by aberrant activation of the immune system that leads to or causes pathogenesis of several acute and chronic conditions including, for example, sarcoidosis, rheumatoid arthritis, inflammatory bowel disease, transplant rejection, colitis, gastritis and ileitis. An inflammatory disease can include a state in which there is a response to tissue damage, cell injury, an antigen, an infectious disease, and/or some unknown cause. Symptoms of inflammation may include, but are not limited to, cell infiltration and tissue swelling.

In the invention, particular preference is given to compounds of Formula I or any subgroup thereof that in the inhibition assay for RIP2 described below inhibit kinase activity with an IC_{50} value of less than 10 μM, preferably less than 1 μM, most preferably less than 100 nM.

Said inhibition may be effected *in vitro* and/or *in vivo,* and when effected *in vivo*, is preferably effected in a selective manner, as defined above.

The term "RIP2 kinase-mediated condition" or "disease", as used herein, means any disease or other deleterious condition in which the RIP2 kinase and/or mutants thereof is/are known to play a role. The term " RIP2 kinase-mediated condition" or "disease" also means those diseases or

conditions that are alleviated by treatment with a RIP2 kinase inhibitor. Accordingly, another embodiment of the present invention relates to treating or lessening the severity of one or more diseases in which the RIP2 kinase is known to play a role.

For pharmaceutical use, the compounds of the invention may be used as a free acid or base, and/or in the form of a pharmaceutically acceptable acid-addition and/or base-addition salt (e.g. obtained with non-toxic organic or inorganic acid or base), in the form of a hydrate, solvate and/or complex, and/or in the form or a pro-drug or pre-drug, such as an ester. As used herein and unless otherwise stated, the term "solvate" includes any combination which may be formed by a compound of this invention with a suitable inorganic solvent (e.g. hydrates) or organic solvent, such as but not limited to alcohols, ketones, esters and the like. Such salts, hydrates, solvates, etc. and the preparation thereof will be clear to the skilled person; reference is for instance made to the salts, hydrates, solvates, etc. described in US-A-6,372,778, US-A-6,369,086, US-A-6,369,087 and US-A-6,372,733.

The pharmaceutically acceptable salts of the compounds according to the invention, i.e. in the form of water-, oil-soluble, or dispersible products, include the conventional non-toxic salts or the quaternary ammonium salts which are formed, e.g., from inorganic or organic acids or bases. Examples of such acid addition salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalene-sulfonate, nicotinate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. In addition, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl–bromides and others. Other pharmaceutically acceptable salts include the sulfate salt ethanolate and sulfate salts.

Generally, for pharmaceutical use, the compounds of the inventions may be formulated as a pharmaceutical preparation or pharmaceutical composition comprising at least one compound of the invention and at least one pharmaceutically acceptable carrier, diluent or excipient and/or adjuvant, and optionally one or more further pharmaceutically active compounds.

By means of non-limiting examples, such a formulation may be in a form suitable for oral administration, for parenteral administration (such as by intravenous, intramuscular or subcutaneous injection or intravenous infusion), for administration by inhalation, by a skin patch, by an implant, by a suppository, etc.. Such suitable administration forms – which may be solid, semi-

solid or liquid, depending on the manner of administration – as well as methods and carriers, diluents and excipients for use in the preparation thereof, will be clear to the skilled person; reference is again made to for instance US-A-6,372,778, US-A-6,369,086, US-A-6,369,087 and US-A-6,372,733, as well as to the standard handbooks, such as the latest edition of Remington's Pharmaceutical Sciences.

Some preferred, but non-limiting examples of such preparations include tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments, creams, lotions, soft and hard gelatin capsules, suppositories, eye drops, sterile injectable solutions and sterile packaged powders (which are usually reconstituted prior to use) for administration as a bolus and/or for continuous administration, which may be formulated with carriers, excipients, and diluents that are suitable per se for such formulations, such as lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, polyethylene glycol, cellulose, (sterile) water, methylcellulose, methyl- and propylhydroxybenzoates, talc, magnesium stearate, edible oils, vegetable oils and mineral oils or suitable mixtures thereof. The formulations can optionally contain other pharmaceutically active substances (which may or may not lead to a synergistic effect with the compounds of the invention) and other substances that are commonly used in pharmaceutical formulations, such as lubricating agents, wetting agents, emulsifying and suspending agents, dispersing agents, desintegrants, bulking agents, fillers, preserving agents, sweetening agents, flavoring agents, flow regulators, release agents, etc.. The compositions may also be formulated so as to provide rapid, sustained or delayed release of the active compound(s) contained therein, for example using liposomes or hydrophilic polymeric matrices based on natural gels or synthetic polymers. In order to enhance the solubility and/or the stability of the compounds of a pharmaceutical composition according to the invention, it can be advantageous to employ α-, β- or γ-cyclodextrins or their derivatives. An interesting way of formulating the compounds in combination with a cyclodextrin or a derivative thereof has been described in EP-A-721,331. In particular, the present invention encompasses a pharmaceutical composition comprising an effective amount of a compound according to the invention with a pharmaceutically acceptable cyclodextrin.

In addition, co-solvents such as alcohols may improve the solubility and/or the stability of the compounds. In the preparation of aqueous compositions, addition of salts of the compounds of the invention can be more suitable due to their increased water solubility.

For local administration, the compounds may advantageously be used in the form of a spray, ointment or transdermal patch or another suitable form for topical, transdermal and/or intradermal administration.

More in particular, the compositions may be formulated in a pharmaceutical formulation comprising a therapeutically effective amount of particles consisting of a solid dispersion of the compounds of the invention and one or more pharmaceutically acceptable water-soluble polymers.

The term "a solid dispersion" defines a system in a solid state (as opposed to a liquid or gaseous state) comprising at least two components, wherein one component is dispersed more or less evenly throughout the other component or components. When said dispersion of the components is such that the system is chemically and physically uniform or homogenous throughout or consists of one phase as defined in thermodynamics, such a solid dispersion is referred to as "a solid solution". Solid solutions are preferred physical systems because the components therein are usually readily bioavailable to the organisms to which they are administered.

It may further be convenient to formulate the compounds in the form of nanoparticles which have a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than 1000 nm. Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants.

Yet another interesting way of formulating the compounds according to the invention involves a pharmaceutical composition whereby the compounds are incorporated in hydrophilic polymers and applying this mixture as a coat film over many small beads, thus yielding a composition with good bio-availability which can conveniently be manufactured and which is suitable for preparing pharmaceutical dosage forms for oral administration. Materials suitable for use as cores in the beads are manifold, provided that said materials are pharmaceutically acceptable and have appropriate dimensions and firmness. Examples of such materials are polymers, inorganic substances, organic substances, and saccharides and derivatives thereof.

The preparations may be prepared in a manner known per se, which usually involves mixing at least one compound according to the invention with the one or more pharmaceutically acceptable carriers, and, if desired, in combination with other pharmaceutical active compounds, when necessary under aseptic conditions. Reference is again made to US-A-6,372,778, US-A-6,369,086, US-A-6,369,087 and US-A-6,372,733 and the further prior art mentioned above, as well as to the standard handbooks, such as the latest edition of Remington's Pharmaceutical Sciences.

The pharmaceutical preparations of the invention are preferably in a unit dosage form, and may be suitably packaged, for example in a box, blister, vial, bottle, sachet, ampoule or in any other suitable single-dose or multi-dose holder or container (which may be properly labeled); optionally with one or more leaflets containing product information and/or instructions for use. Generally, such unit dosages will contain between 1 and 1000 mg, and usually between 5 and 500 mg, of the at least one compound of the invention, e.g. about 10, 25, 50, 100, 200, 300 or 400 mg per unit dosage.

The compounds can be administered by a variety of routes including the oral, rectal, ocular, transdermal, subcutaneous, intravenous, intramuscular or intranasal routes, depending mainly on the specific preparation used and the condition to be treated or prevented, and with oral and intravenous administration usually being preferred. The at least one compound of the invention will generally be administered in an "effective amount", by which is meant any amount of a compound

of Formula or any subgroup thereof that, upon suitable administration, is sufficient to achieve the desired therapeutic or prophylactic effect in the individual to which it is administered. Usually, depending on the condition to be prevented or treated and the route of administration, such an effective amount will usually be between 0.01 to 1000 mg per kilogram body weight day of the patient per day, more often between 0.1 and 500 mg, such as between 1 and 250 mg, for example about 5, 10, 20, 50, 100, 150, 200 or 250 mg, per kilogram body weight day of the patient per day, which may be administered as a single daily dose, divided over one or more daily doses, or essentially continuously, e.g. using a drip infusion. The amount(s) to be administered, the route of administration and the further treatment regimen may be determined by the treating clinician, depending on factors such as the age, gender and general condition of the patient and the nature and severity of the disease/symptoms to be treated. Reference is again made to US-A-6,372,778,US-A-6,369,086, US-A-6,369,087 and US-A-6,372,733 and the further prior art mentioned above, as well as to the standard handbooks, such as the latest edition of Remington's Pharmaceutical Sciences.

In accordance with the method of the present invention, said pharmaceutical composition can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The present invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

For an oral administration form, the compositions of the present invention can be mixed with suitable additives, such as excipients, stabilizers, or inert diluents, and brought by means of the customary methods into the suitable administration forms, such as tablets, coated tablets, hard capsules, aqueous, alcoholic, or oily solutions. Examples of suitable inert carriers are gum arabic, magnesia, magnesium carbonate, potassium phosphate, lactose, glucose, or starch, in particular, corn starch. In this case, the preparation can be carried out both as dry and as moist granules. Suitable oily excipients or solvents are vegetable or animal oils, such as sunflower oil or cod liver oil. Suitable solvents for aqueous or alcoholic solutions are water, ethanol, sugar solutions, or mixtures thereof. Polyethylene glycols and polypropylene glycols are also useful as further auxiliaries for other administration forms. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

When administered by nasal aerosol or inhalation, these compositions may be prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. Suitable pharmaceutical formulations for administration in the form of aerosols or sprays are, for example, solutions, suspensions or emulsions of the compounds of the invention or their physiologically tolerable salts in a pharmaceutically acceptable solvent, such as ethanol or water, or a mixture of such solvents. If required, the formulation can also additionally contain other pharmaceutical auxiliaries such as surfactants, emulsifiers and stabilizers as well as a propellant.

For subcutaneous administration, the compound according to the invention, if desired with the substances customary therefore such as solubilizers, emulsifiers or further auxiliaries are brought into solution, suspension, or emulsion. The compounds of the invention can also be lyophilized and the lyophilizates obtained used, for example, for the production of injection or infusion preparations. Suitable solvents are, for example, water, physiological saline solution or alcohols, e.g. ethanol, propanol, glycerol, in addition also sugar solutions such as glucose or mannitol solutions, or alternatively mixtures of the various solvents mentioned. The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally-acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

When rectally administered in the form of suppositories, these formulations may be prepared by mixing the compounds according to the invention with a suitable non-irritating excipient, 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.

In preferred embodiments, the compounds and compositions of the invention are used orally or parenterally.

The invention will now be illustrated by means of the following synthetic and biological examples, which do not limit the scope of the invention in any way.

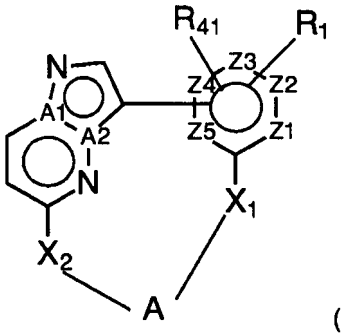
EXAMPLES

A. Compound synthesis and physicochemical properties

The compounds of this invention can be prepared by any of several standard synthetic processes commonly used by those skilled in the art of organic chemistry. The compounds are generally prepared from starting materials which are either commercially available or prepared by standard means obvious to those skilled in the art.

General schemes:

As indicated herein before, the present invention provides compounds according to formula I, for use in the diagnosis, prevention and/or treatment of RIP2-kinase associated diseases:

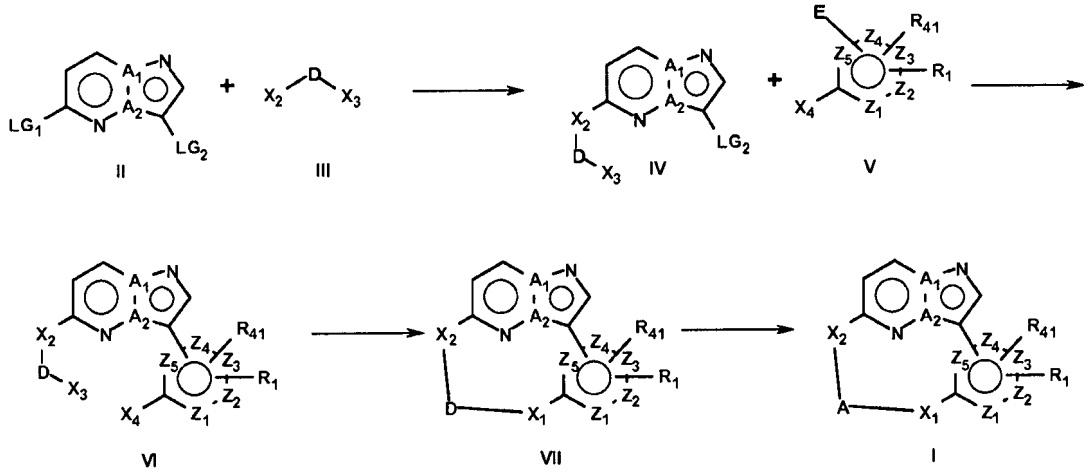


(I)

With reference to the general reaction schemes suitable for preparing said compounds, these compounds can be represented by formulas Ia or Ib respectively, for which the general reaction schemes can be found herein below.

In general the compounds of formula (I) can be prepared as shown in scheme 1 below wherein a pyrazolo[1,5-a]pyrimidine or a imidazo[2,1-f]pyridazine of formula (II) is converted by reaction with a compound of formula (III) into a compound of formula (IV), which is then reacted with a (hetero-) aryl of formula (V) to form a compound of formula (VI). The compound of formula (VI) can then be optionally deprotected if desired before cyclisation to form a compound of formula (VII). The compound of formula (VII) can be optionally converted into a compound of general formula (I).

Scheme 1



In the above scheme:

LG_1 and LG_2 each independently represent suitable leaving or functional groups;

X_3 and X_4 together with the functional moiety to which they are attached represent an unprotected or a protected functional group which upon reaction (after deprotection) produce together X_1 as defined in formula I;

E represents a suitable functional group that can be used to form a direct bond between the (hetero-)aryl group and the scaffold.

D represents a functional group such as A or a protected functional group, which upon further reaction and/or deprotection produces a functional group such as A as defined in formula I;

In the above reaction of the compound of formula (II) with the compound of formula (III) the leaving groups LG_1 and LG_2 are advantageously a halo group such as a chlorine or a bromine group. The reaction can be affected by a substitution for example by treating the compound of formula (II) with the compound of formula (III) in an organic solvent such as acetonitrile with an appropriate base such as for example diisopropylethylamine at an elevated temperature for example under reflux.

Compounds of formula (III) can be obtained through various selective protection and deprotection steps.

The compound of formula (IV) can optionally be protected with a suitable protecting group such as a tert-butyloxycarbonylamino group in a conventional manner for example by treatment with tert-butoxycarbonyl anhydride in basic conditions using for example triethylamine and 4-(dimethylamino)pyridine in a solvent such as tetrahydrofurane at an elevated temperature such as under reflux.

The reaction of the resulting compound (IV) with a (hetero-)aryl compound of formula (V) is advantageously effected through the coupling of a boronic acid E or boronic ester E derivative of the (hetero-)aryl compound under Suzuki conditions using for example tetrakis(triphenylphosphine)palladium(0), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (Xphos) and potassium phosphate tribasic in a solvent mixture such as 1,4-dioxane/water at an elevated temperature for example under reflux.

The resulting compound of formula (VI) can optionally be treated to remove any desired protecting groups for example silyl ether groups such as tert-butyldimethylsilyl groups can be converted to the parent free hydroxy group. Such deprotection can be effected in a conventional manner for example using tetrabutylammonium fluoride in tetrahydrofuran at room temperature. The resulting compound of formula (VI) can also optionally be treated to remove any desired protecting groups for example benzyl groups can be removed in a conventional manner for example using hydrogen gas and palladium on activated charcoal (10%) in a solvent such as methanol at a temperature such as room temperature. The compound of formula (VI) can optionally be treated to remove any desired protecting groups for example tert-butyloxycarbonylamino groups can be converted to the parent free amino group. Such deprotection can be effected in a conventional manner for example by treatment under acidic conditions for example using a 4N acetyl chloride solution in a solvent such as methanol at for example room temperature.

The cyclisation of the compound of formula (VI) can be effected for example under Mitsunobu conditions using for example diisopropyl azodicarboxylate and triphenylphosphine in a solvent mixture such as 2-methyl-1,4-dioxane and toluene at an elevated temperature such as 90°C.

The resulting compound of formula (VII) can optionally be treated to remove any desired protecting groups for example tert-butyloxycarbonylamino groups can be converted to the parent free amino

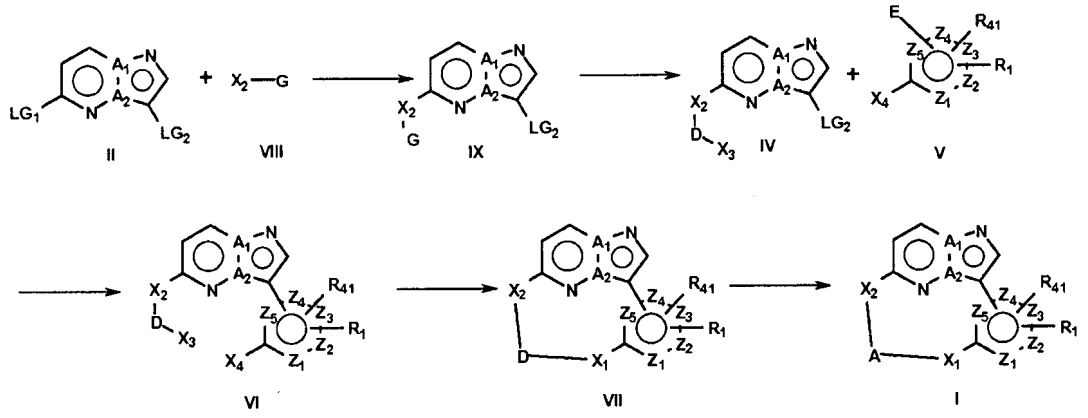
group. Such deprotection can be effected in a conventional manner for example by treatment under acidic conditions for example using a 4N hydrochloric acid solution in methanol at room temperature.

The deprotected compound can optionally be treated to form an amide compound of formula (I). The reaction can advantageously be affected by treatment with an acylchloride and a base such as triethylamine in a solvent such as tetrahydrofuran at room temperature. The reaction can also be affected using for example O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) and diisopropylethylamine in a solvent such as N,N-dimethylformamide at for example room temperature.

Compounds B19, B21, B76, F81, F82, F83, F84, F86, F87, F88, F89, F91 and F92 may be prepared according to the synthesis described in Scheme 1.

The compounds of formula (I) can also be prepared as shown in general scheme 2 below wherein a pyrazolo[1,5-a]pyrimidine or a imidazo[2,1-f]pyridazine of formula (II) is converted by reaction with a compound of formula (VIII) into a compound of formula (IX). The compound of formula (IX) can be optionally be converted into a compound of formula (IV) which is then reacted with a (hetero-)aryl of formula (V) to form a compound of formula (VI). The compound of formula (VI) can then be optionally deprotected if desired before cyclisation to form a compound of formula (VII). The compound of formula (VII) can be optionally converted into a compound of general formula (I).

Scheme 2



In the above scheme:

LG_1 and LG_2 each independently represent suitable leaving or functional groups;

E represents a suitable functional group that can be used to form a direct bond between the (hetero-)aryl group and the scaffold.

G represents a suitable functional group or protected functional group, which upon further reaction and/or deprotection produces a functional group such as D;

D represents a functional group such as A or a protected functional group, which upon further reaction and/or deprotection produces a functional group such as A as defined in formula I;

In the above reaction of the compound of formula (II) with the compound of formula (VIII) the leaving groups LG_1 and LG_2 are advantageously a halo group such as a chlorine or a bromine group. The reaction can be affected by a substitution for example by treating the compound of formula (II) with the compound of formula (VIII) in an organic solvent such as tetrahydrofuran with an appropriate base such as for example sodium hydride at for example room temperature.

Compounds of formula (VIII) can be either commercially acquired or obtained through various selective protection and deprotection steps.

The compounds of formula (IX) can be deprotected using for example acidic conditions such as a 4N hydrochloric acid solution in methanol at room temperature.

The compounds of formula (IX) can be converted into compounds of formula (IV) by using for example a reductive amination. The reaction can be affected by treating the compound of formula (IX) with an alhyde in the presence of a reducing agent such as sodium triacetoxy borohydride and a base such as triethylamine in a solvent such as dichloromethane at for example room temperature.

The reaction of the compound with formula (IV) with a (hetero-)aryl compound of formula (V) is advantageously effected under Suzuki conditions using for example tetrakis(triphenylphosphine)palladium(0) and potassium phosphate tribasic in a solvent mixture such as 1,4-dioxane/water at an elevated temperature for example 80°C.

The resulting compound of formula (VI) can optionally be treated to remove any desired protecting groups for example silyl ether groups such as tert-butyldimethylsilyl groups can be converted to the parent free hydroxy group. Such deprotection can be effected using for example acetic acid in tetrahydrofuran at for example room temperature. The compound of formula (VI) can optionally be treated to remove any desired protecting groups for example tert-butyloxycarbonylamino groups can be converted to the parent free amino group. Such deprotection can be effected in a conventional manner for example by treatment under acidic conditions for example using a 4N acetyl chloride solution in a solvent such as methanol at for example room temperature.

The free hydroxyl group can be converted into a leaving group such as a chloride by reacting the hydroxyl group for example with thionyl chloride in the presence of a base such as pyridine in a solvent such as dichloromethane at an elevated temperature for example under reflux.

The cyclisation of the compound of formula (VII) can be advantageously effected under Williamson conditions using a base such as cesium carbonate in a solvent such as N,N-dimethylformamide at an elevated temperature such as 90°C. Other condtions that can be used for the cyclisation of the compound of formula (VII) can be for example by treatment with O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) and N,N-diisopropylethylamine in a solvent such as N,N-dimethylformamide at for example room temperature.

The resulting compound of formula (VII) can optionally be treated to form a compound of formula (I).

Compound B74 may be prepared according to the synthesis described in Scheme 2.

The compounds of formula (I) can also be prepared as shown in general scheme 3 below wherein a pyrazolo[1,5-a]pyrimidine or a imidazo[2,1-f]pyridazine of formula (II) is converted by reaction with a compound of formula (VIII) into a compound of formula (IX). The compound of formula (IX) can be optionally reacted with a (hetero-)aryl of formula (V) to form a compound of formula (X). The compound of formula (X) can be converted into the compounds of formula (XI). The compound of formula (XI) can then be optionally deprotected if desired before cyclisation to form a compound of formula (VII). The compound of formula (VII) can be optionally converted into a compound of general formula (I).

In the below scheme 3:

LG_1 and LG_2 each independently represent suitable leaving or functional groups;

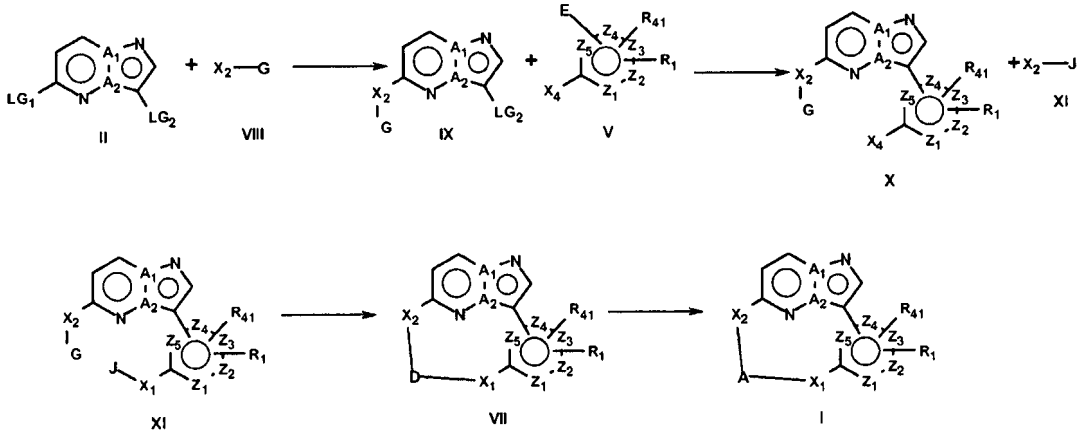
X_4 and X_5 together with the functional moiety to which they are attached represent an unprotected or a protected functional group which upon reaction (after deprotection) produce together X_1 as defined in formula I;

E represents a suitable functional group that can be used to form a direct bond between the (hetero-)aryl group and the scaffold.

G and J represent functional groups or protected functional groups, which upon further reaction and/or deprotection produce a functional group such as D;

D represents a functional group such as A or a protected functional group, which upon further reaction and/or deprotection produces a functional group such as A as defined in formula I;

Scheme 3



In the above reaction of the compound of formula (II) with the compound of formula (VIII) the leaving groups LG_1 and LG_2 are advantageously a halo group such as a chlorine or a bromine group. The reaction can be affected by a substitution for example by treating the compound of formula (II) with the compound of formula (VIII) in an organic solvent such as acetonitrile with an appropriate base such as for example diisopropylethylamine at an elevated temperature for example under reflux.

Compounds of formula (VIII) and (XI) can be either commercially acquired or obtained through various selective protection and deprotection steps.

The resulting compound of formula (IX) can optionally be protected with a suitable protecting group such as a tert-butyloxycarbonylamino group in a conventional manner for example by treatment with tert-butoxycarbonyl anhydride in basic conditions using for example triethylamine and 4-(dimethylamino)pyridine in a solvent such as tetrahydrofuran at an elevated temperature such as under reflux.

The reaction of the resulting compound (IX) with a (hetero-)aryl compound of formula (V) is advantageously effected through the coupling of a boronic acid E or boronic ester E derivative of the (hetero-)aryl compound under Suzuki conditions using for example tetrakis(triphenylphosphine)palladium(0), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (Xphos) and potassium phosphate tribasic in a solvent mixture such as 1,4-dioxane/water at an elevated temperature for example 80°C.

The reaction of the resulting compound of formula (X) with a compound of formula (XI) which can be advantageously effected under Williamson conditions using a base such as potassium carbonate in a solvent such as acetonitrile at an elevated temperature such as under reflux. This reaction can also be effected under Mitsunobu conditions using for example diisopropyl azodicarboxylate and triphenylphosphine in a solvent such as tetrahydrofuran at an elevated temperature such as 90°C.

The resulting compound of formula (XI) can optionally be treated to remove any desired protecting groups for example tert-butyloxycarbonylamino groups can be converted to the parent free amino group and for example ester groups can be converted to the parent free carboxylic acid groups. Such deprotection can be effected in a conventional manner for example by treatment under acidic conditions for example using an aqueous 6N hydrochloric acid solution in a solvent such as acetoniitrile at an elevated temperature for example 60°C or using an acid such as trifluoroacetic acid in a solvent such as dichloromethane at for example room temperature.

The cyclisation of the compound of formula (XI) can be effected for example by treatment with O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) and N,N-diisopropylethylamine in a solvent such as N,N-dimethylformamide at for example room temperature.

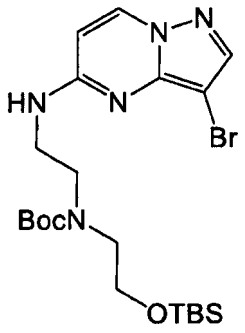
The resulting compound of formula (VII) can optionally be treated to form a compound of formula (I).

Compounds B36, B48, F105, F106 and F108 may be prepared according to the synthesis described in Scheme 3.

The above general processes are illustrated by the specific processes which are described in the patent applications WO2013/045653 A1 and WO2013/046029 A1.

Preparation of intermediate F78

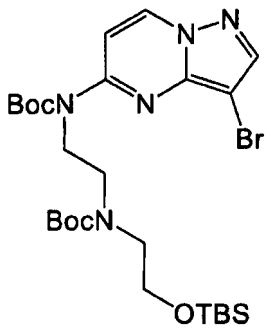
Intermediate F78 is prepared following general scheme 1.



Step A

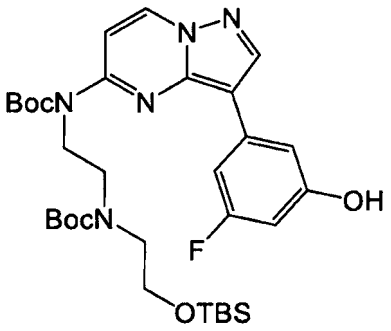
To a solution of 3-bromo-5-chloropyrazolo[1,5-a]pyrimidine (14.0g, 60.22mmol, 1eq), the linker (synthesis described in the patent WO2013/045653 A1; preparation of intermediate 21) (21.1g, 66.24mmol, 1.1eq) and DIPEA (13.67ml, 78.29mmol, 1.3eq) in acetonitrile (180ml) was heated at 70 / 80 °C for 18h. Upon completion, monitored by TLC plate, the reaction mixture was concentrated. The residue was dissolved in EtOAc and washed 2x with water and once with Brine. The organic layer was dried (MgSO4), filtered, concentrated. The crude product was further purified by flash chromatography using a eluent a gradient: Heptane:EtOAc 100:0 to 80:20 fast to 60:40 slow. The product fractions were collected and concentrated to obtain 23.6g of a brown solid (76% yield).

MH+: 514.2/516.2



Step B

The title compound from step A, Boc anhydride (15.01g, 68.8mmol, 1.5eq) and DMAP (0.28g, 2.29mmol, 0.05eq) were dissolved in THF (137ml) and the mixture was heated at 65 °C for 4h. Upon completion, monitored by TLC plate, the reaction mixture was concentrated. The crude product was further purified by flash chromatography using as eluent a gradient: Heptane:EtOAc 100:0 to 50:50 fast 6c volumes. The product fractions were collected and concentrated to obtain 27.0g of brown oil (96% yield).

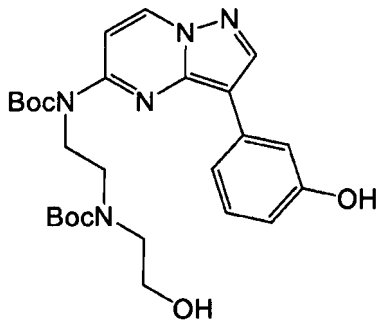


Step C

A mixture of the title compound from step B, (3-fluoro-5-hydroxyphenyl)boronic acid (1.78g, 11.39mmol, 1.0eq), XPhos (0.32g, 0.68mmol, 0.06eq) and potassium phosphate (7.2g, 33.92mmol, 3.0eq) were dissolved in Dioxane /water 3:1 and degassed with N2. Then Palladium Tetrakis (0.39g, 0.34mmol, 0.03eq) was added to the stirring solution. The resulting reaction mixture was stirred at 80°C for 6h under N2 atmosphere. To reach completion, additional amounts of the Boronic acid (1.0eq), Palladium Tetrakis (0.03eq) and XPhos (0.06eq) were added. The reaction mixture was stirred for an additional 18h at 90°C.

The mixture was diluted with EtOAc and the layers were separated. The organic layer was washed 2x with water and once with Brine, dried (MgSO4), filtered, concentrated. The crude product was further purified by flash chromatography using as eluent a gradient: Heptane:EtAOc. 100:0 to 60:40. The product fractions were collected and concentrated to obtain 7.2g of a solid (98% yield).

MH+:546.3

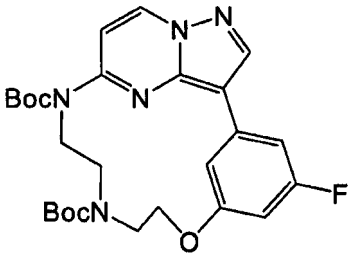


Step D

To a solution of the title compound from Step C in THF (33ml) was added a solution of TBAF 1M in THF (14.5ml, 14.5mmol). The reaction mixture was stirred for 18h at RT, and then the solvent was

concentrated to dryness. The residue was dissolved in Ethyl acetate and washed 3times with water and once with brine. The organic layer was dried over Magnesium sulfate, filtered, concentrated. The crude product was further purified by flash chromatography (n-Hp:EA 0:20 to 30:70) to obtain the title compound as a white solid (5.0g, 84% yield).

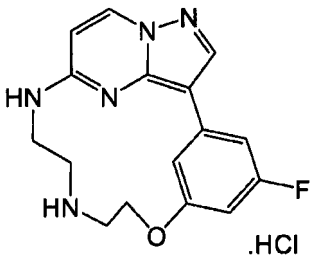
MH+:432.2



Step E

To a stirring solution of Triphenylphosphine (7.66g, 29.22mmol) in Toluene (44ml) at 90°C were simultaneously added a solution of the title compound from Step D (5.0g, 9.74mmol) in 2-MeTHF (11.6ml) and a solution of DIAD (5.79ml, 29.22mmol) in Toluene (11.6ml) over 5h. The resulting mixture was further stirred at 90°C for 30 minutes. The reaction mixture was concentrated to dryness and directly engaged in the next step without purification.

MH+: 514.3



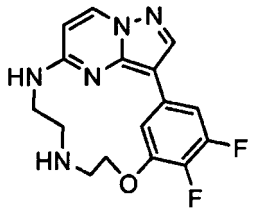
Step F

To the title compound from step E (9.8g, 19.08mmol) was added a 4M solution of HCl in MeOH (57ml). The resulting mixture was stirred at RT for 18h then at 40°C for 8h. At RT the white slurry was filtered off and washed with diisopropylether. The solid was dried under vacuum to obtain the title compound as a white solid (3.0g, 88% yield over 2 steps).

Melting point: >300°C, decomposition

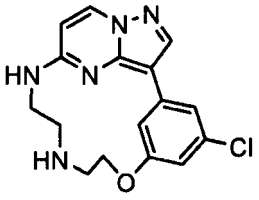
MH+: 314.10

Preparation of intermediate F79



is prepared following general scheme 1 and according to the procedures described in the patent application WO2013/045653 A1 to obtain example 17.

Preparation of intermediate F80

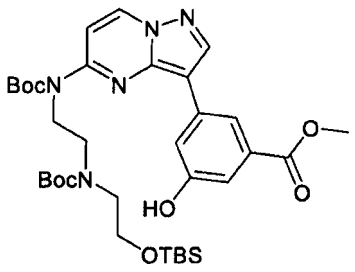


is prepared following general scheme 1 and according to the procedures described in the patent application WO2013/045653 A1 to obtain example 17.

Examples F81 to F89 were prepared following general scheme 1 and according to the procedures described in the patent application WO2013/045653 A1 to obtain example 6.

Preparation of intermediate F90

Intermediate F90 is prepared following general scheme 1

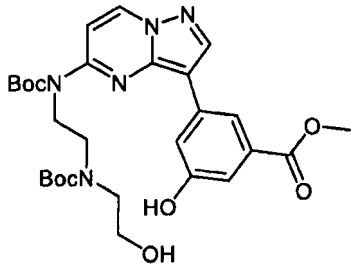


Step A

A mixture of Dioxane and water (3:1) (148ml) was placed in a flask and degased by bubbling nitrogen gas. Then the title compound from Example F78 step B (15g, 24.4mmol, 1.0eq), the Boronic ester (8.82g, 31.73mmol, 1.3eq), Palladium Tetrakis (.568g, 0.49mmol, 0.02eq), XPhos (0.93g, 1.95mmol, 0.08eq) and Potassium phosphate (25.9g, 5.0eq) were added and the suspension was stirred at 85 °C under nitrogen for 15 hours. Upon completion, monitored by LCMS, Dioxane was removed, water was added and the product was extracted with ethyl acetate. The organic layer was

dried over magnesium sulfate, filtered and the filtrate was concentrated under reduce pressure. The product was purified by flash chromatography on silica gel using as eluents mixtures of heptane: ethyl acetate (from 0 % to 33 % of ethyl acetate). The product fractions were collected and the solvent was evaporated to dryness. The title compound was obtained as a solid (13.43g, 80.2% yield).

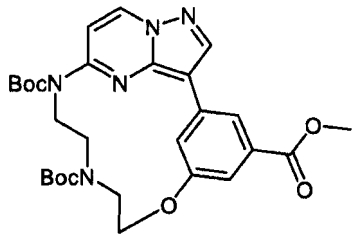
MH+: 586.1



Step B

A solution of the title compound from step C and 1M TBAF (21.54ml, 1eq) in THF (59ml) was stirred at r.t. for 1 hour. Upon completion, monitored by LCMS, solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate, washed with water (x3) and brine. Organic layer was washed with brine, dried over magnesium sulfate and evaporated to dryness. The product was used as such in the next reaction step.

MH+: 572.0

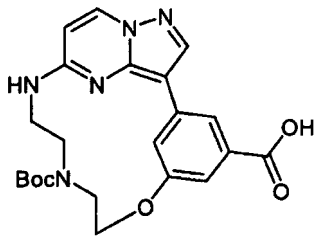


Step C

The reaction was performed in parallel in 2 batches.

A solution of the title compound from step D (8.95g, 15.65mmol) in 2-methyl THF (20 ml/mmol) and a solution of DIAD (9.31ml, 46.95mmol, 3.0eq) in toluene (same volume) were simultaneously added to a solution of Triphenylphosphine (12.31g, 46.95mmol, 3.0eq) in toluene (75 ml/mmol of starting material A) at 90°C for 3 hours. After that, the reaction mixture was heated for 30 minutes. Upon completion, monitored by LCMS, solvent was evaporated and the product was purified by flash chromatography on silica gel using as eluents mixtures of dichloromethane: methanol (from 0 % to 10 % of methanol). The product fractions were collected and the solvent was evaporated to dryness to lead the expected compound in 7.7g, 88% yield.

MH+: 554.0



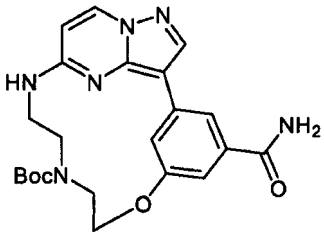
Step D

A mixture of the title compound from step E (1.5g, 2.71mmol, 1.0eq) and lithium hydroxide hydrate (0.34g, 8.13mmol, 3.0eq) were suspended in THF/MeOH/H2O (2:2:1) (25ml). The mixture was stirred at 50 °C for 15 hours. Upon completion, monitored by LCMS, solvent was removed. Water was added and HCl 1M was added to acidify the solution to pH 6. The resulting solid was filtered and washed with methanol, then dried at high vacuum (615mg).

The product in the aqueous phase was extracted with dichloromethane. The organic layer was dried over magnesium sulfate, filtered and the filtrate was concentrated under reduce pressure. The product was purified by flash chromatography on silica gel using as eluents mixtures of DCM:MeOH (from 0 % to 100% of methanol) and then dichloromethane: methanol (from 0 to 10 % of methanol).

The title compound was obtained as a white solid (917mg, 77% yield)

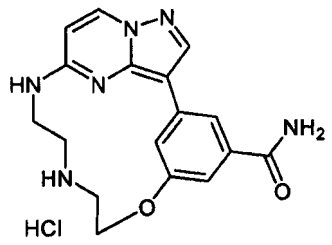
MH+: 440.0



Step E

HBTU (0.637g, 1.68mmol, 1.2eq) was added to a solution of the title compound from step F (0.615mg, 1.40mmol, 1.0eq), Ammonium chloride (0.08g, 1.40mmol, 1.10eq) and DIPEA (0.595ml, 3.50mmol, 2.5eq) in DMF (4ml). The mixture was stirred at RT for 19 hours. Upon completion, monitored by LCMS, the reaction was diluted with ethyl acetate and washed with NaHCO3 saturated solution. The organic layer was dried over magnesium sulfate, filtered and the filtrate was concentrated under reduce pressure. The product was purified by flash chromatography on silica gel using as eluents mixtures of heptane:ethyl acetate (from 0 % to 100 % of ethyl acetate). The product fractions were collected and the solvent was evaporated to dryness to lead the title compound as a solid (507mg, 82%).

MH+: 439.0



Step F

The title compound from step G (507mg, 1.16mmol, 1.0eq) was stirred in 4M HCl in Dioxane (3.5ml) at room temperature for 3 hours. Upon completion, monitored by LCMS, solvent was removed. Ethyl ether was added and the solid formed was filtered of and dried under vacuum to lead the title compound as white solid (372mg, 85%).

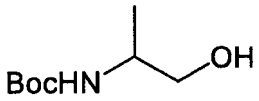
MH+: 339.0

HPLC retention time: 0.197min

Melting point:

Examples F91 to F92 were prepared following general scheme 1 and according to the procedures described in the patent application WO2013/045653 A1 to obtain example 6.

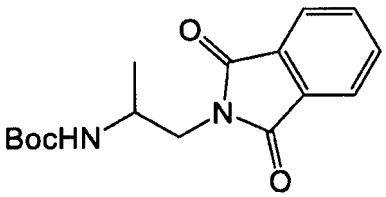
Preparation of intermediate F104



Step A

Boc anhydride (15.98g, 73.23mmol, 1.1eq) was added to a solution of 2-aminopropan-1-ol (5.0g, 66.57mmol, 1.0eq) in CH2Cl2 (200ml). The mixture was stirred at room temperature for 1 hour. Upon completion, monitored by TLC plate, the product was purified by flash chromatography on silica gel using as eluents mixtures of heptane: ethyl acetate (from 0 % to 50 % of ethyl acetate). The product fractions were collected and the solvent was evaporated to dryness to lead the title compound in 10.89g (93% yield).

MH+: 198.1 (M+H+Na)

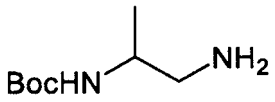


Step B

The title compound from step A (10.89g, 62.13mmo, 1.0eq) and Pthalimide (13.71g, 93.2mmol, 1.5eq) were dissolved in anhydrous THF (167 ml). The reaction was degassed and

Triphenylphosphine (24.44g, 93.2mmol, 1.5eq) was added. The reaction was cooled to 0°C under N2 atmosphere. DIAD (18.84g, 93.19mmol, 1.5eq) was diluted with 20 ml of THF and added dropwise (exothermic). When the addition was completed, the reaction was allowed to reach room temperature and stirred for 90 minutes. Upon completion, monitored by LCMS, solvent was removed, acetonitrile was added, heated until complete solution and then cooled. The solid thus formed was filtered and dried under vacuum to lead a first fraction in 7.68g.

The product in the mother liquor was purified by flash chromatography on silica gel using as eluents mixtures of heptane: ethyl acetate (from 0 % to 50 % of ethyl acetate). The product fractions were collected and the solvent was evaporated to dryness to lead the title compound as a solid in 7.892g. It contains same impurities related with DIAD.

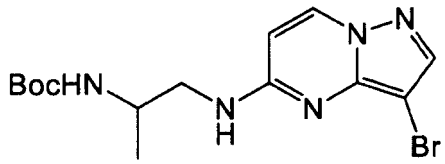


Step C

A solution of the title compound from step B (9.0g, 29.57mmol, 1.0eq) and Hydrazine hydrate (2.76ml, 88.71mmol, 3.0eq) in ethanol (89ml) was stirred at 70°C for 4 hours. Upon completion, monitored by LCMS, the reaction mixture was cooled to RT; the resulting suspension was filtered to remove the white solid formed. The filtrate was then evaporated and the residue was dissolved in ethyl acetate, washed with NaOH 1M and brine. Organic layer was dried, filtered and concentrated to give the title compound as colorless oil, which was used as such in the next synthetic step.

Example F105

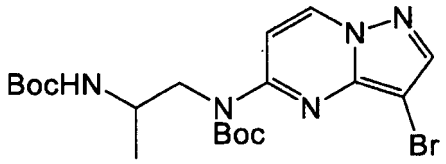
Example F105 was prepared following general scheme 3



Step A

A solution of 3-bromo-5-chloropyrazolo[1,5-a]pyrimidine (3.0g, 12.9mmol, 1.0eq), the intermediate F104 (4.49g, 25.8mmol, 2.0eq) and DIPEA (4.61ml, 27.09mmol, 2.1eq) in acetonitrile (39ml) was refluxed for 15 hours. Upon completion, monitored by LCMS, solvent was removed. Ethyl acetate was added and washed with water. The organic layer was dried over magnesium sulfate, filtered and the filtrate was concentrated under reduce pressure. The product was purified by flash chromatography on silica gel using as eluents mixtures of heptane: ethyl acetate (from 0 % to 66 % of ethyl acetate). The product fractions were collected and the solvent was evaporated to dryness to lead the title compound as a solid in 4.04g (84.5% yield).

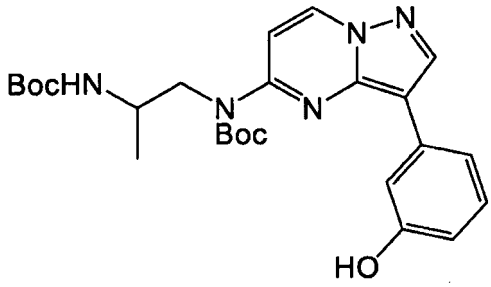
MH+: 370.1/372.1



Step B

Boc anhydride (2.59g, 11.86mmol, 1.1eq) was added to a mixture of the title compound from step A (3.99g, 10.78mmol, 1.0eq), Triethylamine (1.79ml, 12.94mmol, 1.2eq) and DMAP (66mg, .54mmol, 0.05eq) in THF (32ml). The solution was refluxed for 150 minutes. Upon completion, monitored by LCMS, solvent was removed. Water was added and the product was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and the filtrate was concentrated under reduce pressure. The product was purified by flash chromatography on silica gel using as eluents mixtures of heptane: ethyl acetate (from 5 % to 40 % of ethyl acetate). The product fractions were collected and the solvent was evaporated to dryness to lead the title compound in 4.63g (91% yield).

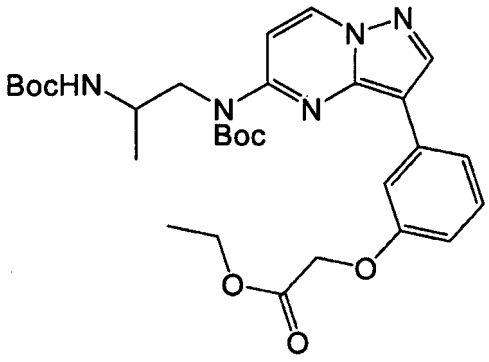
MH+: 492.1/494.1



Step C

A mixture of Dioxane and Water (3:1) (126ml) was placed in a flask and degased by bubbling nitrogen gas. Then the title compound from step B (4.63g, 9.84mmol, 1.0eq), 3-hydroxyphenyl Boronic acid (1.76g, 12.79mmol, 1.3eq), Palladium Tetrakis (228mg, 0.197mmol, 0.02eq), XPhos (377mg, 0.79mmol, 0.08eq) and Potassium phosphate (0.223g, 49.2mmol, 5.0eq) were added and the suspension was stirred at 85 °C under nitrogen for 3 hours. Upon completion, monitored by LCMS, Dioxane was removed. Water was added and the product was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and the filtrate was concentrated under reduce pressure. The product was purified by flash chromatography on silica gel using as eluents mixtures of dichloromethane: methanol (from 100:0 to 20:1). The product fractions were collected and the solvent was evaporated to dryness to lead the title compound in 4.39g (92% yield). It contains some OPPH3.

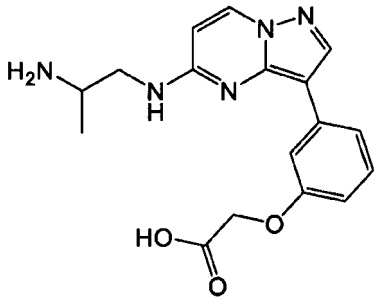
MH+: 484.3



Step D

A mixture of the title compound from step C (1.5g, 3.1mmol, 1.0eq), ethyl 2-bromoacetate (514ul, 4.65mmol, 1.5eq), Potassium carbonate (857mg, 6.2mmol, 2.0eq) and Potassium iodide (27mg, 0.16mmol, 0.05eq) were heated at 80 ª C for 2 hours in DMF (9.3ml). Upon completion, monitored by LCMS, water was added and the product was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and the filtrate was concentrated under reduce pressure. The product was purified by flash chromatography on silica gel using as eluents mixtures of heptane: ethyl acetate (from 5 % to 33 % of ethyl acetate). The product fractions were collected and the solvent was evaporated to dryness to lead the title compound in 1.31g (74% yield).

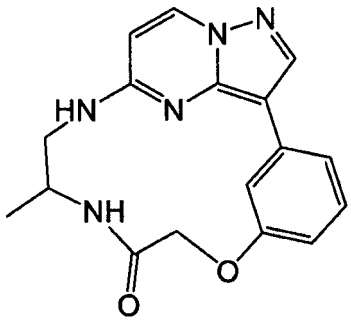
MH+: 592.3



Step E

To a solution of the title compound from step D (1.31g, 2.29mmol, 1.0q) in THF (12 ml/mmol) (6.87ml) was added HCl 6M (12 ml/mmol). The mixture was stirred at 60 °C in a sealed tube for 3 hours. Upon completion, monitored by LCMS, solvent was removed. Toluene/THF (1:1) was added and evaporated. Then toluene was added and evaporated and finally ethanol was added and evaporated. The crude was dried under vacuum and used as such in the next reaction step.

MH+: 342.2



Step F

A suspension of the title compound from step E (2.02mmol) and DIPEA (1.72ml, 10.1mmol, 5.0eq) in DMF (60ml) was added dropwise to a solution of HATU (2.3g, 6.06mmol, 3.0eq) and DIPEA (5.15ml, 30.3mmol, 15.0eq) in DMF (40ml) at room temperature for 3 hours. Upon completion, monitored by LCMS, Ammonia 7N in methanol was added and stirred for 30 minutes. Solvent was removed and the product was purified by flash chromatography on silica gel using as eluents mixtures of dichloromethane: methanol (from 100:0 to 20:1). The product fractions were collected and the solvent was evaporated to dryness. The product pure was precipitated with acetonitrile and dried under vacuum to lead a pale solid in 463mg (71% yield).

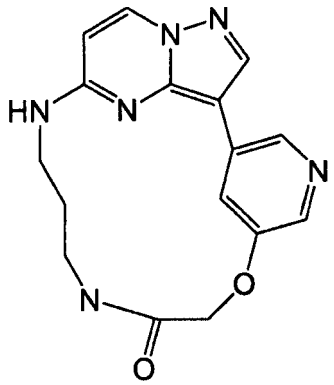
MH+: 324.2

Retention time: 2.107min

Fusion point: >300 °C.

Example F106

Example F106 was prepared following general scheme 3 and more precisely a similar procedure than for the example F105.



Yield: 5mg, 2.9%

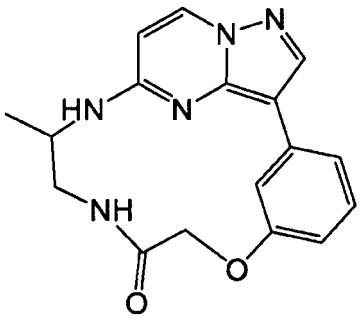
MH+: 325.2

Retention time: 1.343min

Melting point: ND

Preparation of intermediate F107

Intermediate F107 was prepared following general scheme 3

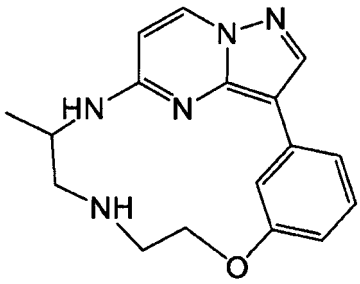


The title compound was prepared following a similar procedure than for the example F129.

MH+: 324.2

Example F108

Example F108 was prepared following general scheme 3



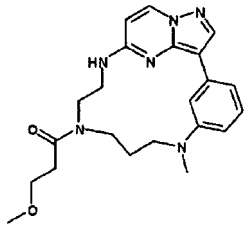
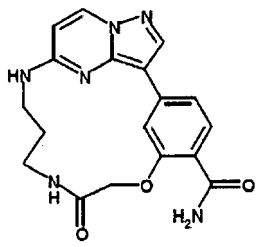
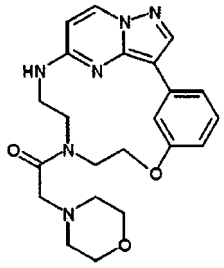
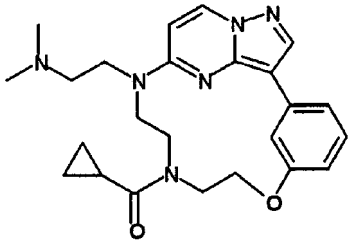
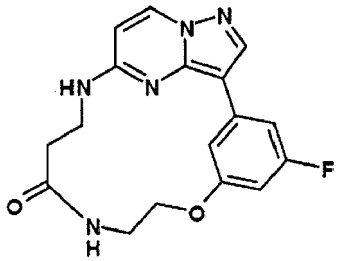
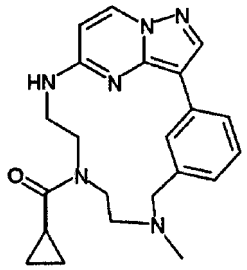
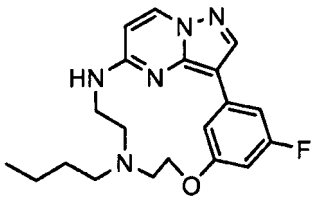
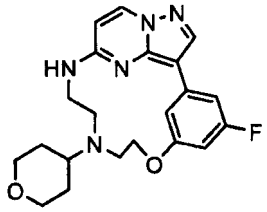
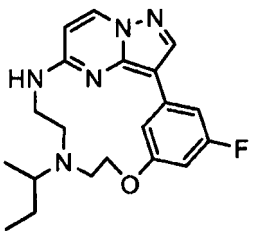
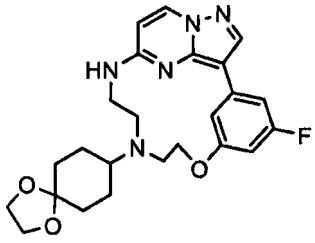
Step A

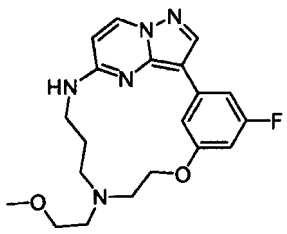
The intermediate F107 (163mg, 0.5mmol, 1.0eq) was dissolved in Borane dimethylsulfide 2M in THF (0.38ml, 5.0mmol, 10.0eq) and THF (1.5ml), gas evolved. The reaction mixture was stirred for 32h at rt. Upon completion, monitored by LCMS, the reaction mixture was quenched with 2N HCl and heated for 1h at 100°C (THF evaporated). The product was extracted with DCM 2x and once with DCM:MeOH 9:1. The combined organic layers were concentrated. The crude was purified by flash chromatography using a mixture of DCM:MeOH 98:2 to 95:5 slow. The compound was further purified by PREP HPLC to lead the title compound in 47mg (30% yield).

MH+: 310.2

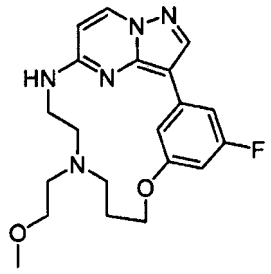
Retention time: 1.952

Table 1

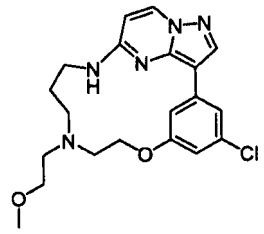
 Compound B19, Example B16	 Compound B21, example B61
 Compound B36, Example B23	 Compound B48, Example B35
 Compound B74, Example B63	 Compound B76, Example B65
 Compound F81, Example F81	 Compound F82, Example F82
 Compound F83, Example F83	 Compound F84, Example F84



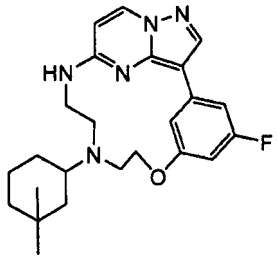
Compound F86, Example F86



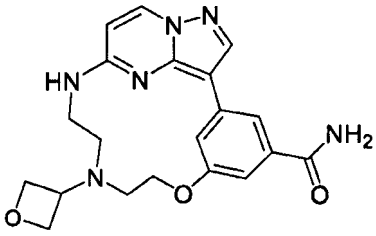
Compound F87, Example F87



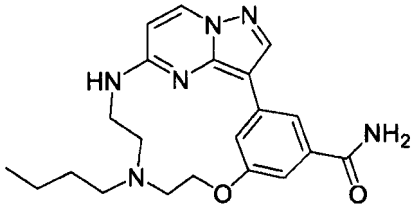
Compound F88, Example F88



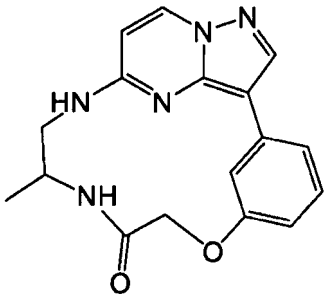
Compound F89, Example F89



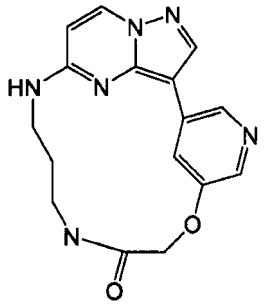
Compound F91, Example F91



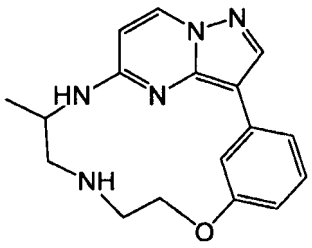
Compound F92, Example F92



Compound F105, Example F105



Compound F106, Example F106



Compound F108, Example F108

The compounds were identified according to the analytical methods and the analytical results described in WO2013/045653 A1 and WO2013/046029 A1.

Table 2: Melting points

COMPOUND N°	MELTING POINT (°C)
F81	370.2
F82	398.4
F83	370.4
F84	454.3
F86	386.2
F87	386.2
F88	402.1
F89	423.3
F91	395.2
F92	395.2
F105	324.2
F106	325.2
F108	310.2

Table 3: LCMS data

COMPOUND NUMBER	MASS $(MH)^+$ PEAK	RETENTION TIME (min)	LCMS METHOD
F81	370.2	2.549	2
F82	398.4	2.297	2
F83	370.4	2.385	2
F84	454.3	2.410	2
F86	386.2	2.083	2
F87	386.2	2.131	2
F88	402.1	2.252	2
F89	423.3	2.942	2
F91	395.2	1.789	2
F92	395.2	1.633	2
F105	324.2	2.107	2
F106	325.2	1.343	2
F108	310.2	1.952	2

The inhibition of RIP2 kinase was assessed using RIP2 recombinant protein in an *in vitro* peptide-based kinase assay.

B. Kinase Activity Assay

The inhibition of RIP2 kinase was assessed using RIP2 recombinant protein in an *in vitro* peptide-based kinase assay.

Protocol

A radiometric protein kinase assay (^{33}PanQinase® Activity Assay) is used for measuring the kinase activity. All assays are performed in 96-well FlashPlates™ from Perkin Elmer in a 50 µl reaction volume. The reaction cocktail is pipetted in 4 steps in the following order:

10 µl of non-radioactive ATP solution (in H2O)
25 µl of assay buffer/ [γ-^{33}P]-ATP mixture
5 µl of test sample in 10% DMSO
10 µl of enzyme/substrate mixture

The assay for RIP2 contains 70 mM HEPES-NaOH pH 7.5, 3 mM $MgCl_2$, 3 mM $MnCl_2$, 3 µM Na-orthovanadate, 1.2 mM DTT, 50 µg/ml PEG20000, ATP (3,0 µM), [γ-^{33}P]-ATP (approx. 5 x 10^{05} cpm per well), protein kinase RIP2 (15,7 nM) and substrate (RBER-Chktide), 2,0 µg/50 µl).
The reaction cocktails were incubated at 30° C for 60 minutes. The reaction was stopped with 50 µl of 2 % (v/v) H_3PO_4, plates were aspirated and washed two times with 200 µl 0.9 % (w/v) NaCl. Incorporation of ^{33}Pi (counting of "cpm") was determined with a microplate scintillation counter.

Compounds

The compounds are dissolved to 10 mM in DMSO. Where needed, solutions are sonicated in a bath sonicator.

Table 4 provides the pIC_{50} values and % Remaining activity values at two concentrations (1 µM and 0,1 µM) of the compounds according to the invention, obtained using the above mentioned kinase assay.

Table 4

Compound N°	IC_{50} for RIP2	%Remaining RIP2 activity at 1 µM	%Remaining RIP2 activity at 0,1 µM
B19		**	**
B21	+++	**	**
B36	+++	**	**
B48	+++	**	**
B74	++	**	**
B76	++	**	*
F81	+++	**	**
F82	+++	**	**
F83	+++	**	**
F84	++	**	**
F86	+++	**	**
F87	+++	**	**
F88	+++	**	**
F89	++	**	**
F91	+++	**	**
F92	+++	**	**
F105	++	**	*
F106	++	ND	ND
F108	++	ND	ND

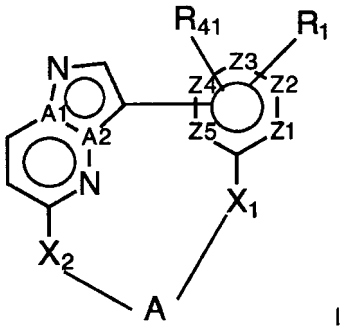
+ indicates an IC50 > 1µM, ++ indicates an IC50 of between 100 nM and 1µM, and +++ indicates an IC50 < 100nM

* indicates a % remaining kinase activity above 50%, ** indicates a % remaining kinase activity below 50%

ND = Not determined

CLAIMS

1. A compound of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof,



I

Wherein

A_1 and A_2 are selected from C and N; wherein when A_1 is C, then A_2 is N; and wherein when A_2 is C, then A_1 is N;

R_1 and R_{41} are each independently selected from –H, –halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -NR_9R_{10}, -(C=O)-R_4, -(C=S)-R_4, -SO_2-R_4, -CN, -NR_9-SO_2-R_4, -C_{3-6}cycloalkyl, -Ar_7 and –Het_1; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, -$NR_{11}R_{12}$, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;

R_2 is selected from –H, -halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -(C=O)-C_{1-6}alkyl, -(C=S)-C_{1-6}alkyl, -(C=O)-O-C_{1-6}alkyl, -(C=S)-O-C_{1-6}alkyl, -(C=O)-$NR_{27}R_{28}$, -(C=S)-$NR_{27}R_{28}$, -C_{3-6}cycloalkyl, -Het_3, -Ar_2, -(C=O)-Het_3, -(C=S)-Het_3, -(C=O)-Ar_2, -(C=S)-Ar_2, -(C=O)-C_{3-6}cycloalkyl, -(C=S)-C_{3-6}cycloalkyl, and -SO_2-C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_3, -Ar_2, and -$NR_{13}R_{14}$;

R_3 is selected from –H, -halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -(C=O)-C_{1-6}alkyl, -(C=S)-C_{1-6}alkyl, -(C=O)-O-C_{1-6}alkyl, -(C=S)-O-C_{1-6}alkyl, -(C=O)-$NR_{29}R_{30}$, -(C=S)-$NR_{29}R_{30}$, -C_{3-6}cycloalkyl -Het_2, -Ar_3, -(C=O)-Het_2, -(C=S)-Het_2, -(C=O)-Ar_3, -(C=S)-Ar_3, -(C=O)-C_{3-6}cycloalkyl, -(C=S)-C_{3-6}cycloalkyl and -SO_2-C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Het_2, -Ar_3, and -$NR_{15}R_{16}$;

R_4 is independently selected from –halo, –OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -$NR_{17}R_{18}$, -C_{3-6}cycloalkyl, -Ar_8 and -Het_4;

R_5 and R_7 are each independently selected from –H, -OH, -halo, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_9, -Ar_1, -C_{3-6}cycloalkyl, -SO_2-Ar_1, -SO_2, -SO_2-C_{1-6}alkyl, -(C=O), -(C=O)-C_{1-6}alkyl, -(C=S), -(C=S)-C_{1-6}alkyl, -O-(C=O)-C_{1-6}alkyl, -O-(C=S)-C_{1-6}alkyl, -(C=O)-O-C_{1-6}alkyl, and -(C=S)-O-C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Ar_1, -Het_9, and -$NR_{23}R_{24}$;

R_6 is selected from -C_{1-6}alkyl, -SO_2, -SO_2-C_{1-6}alkyl, -SO_2-C_{3-6}cycloalkyl, -(C=O), -(C=O)-C_{1-6}alkyl, -(C=O)-C_{2-6}alkenyl, -(C=O)-O-C_{1-6}alkyl, -(C=O)-Het_6, -(C=O)-Ar_6, -(C=O)-C_{3-6}cycloalkyl, -(C=O)-$NR_{31}R_{32}$, -(C=O)-NR_{31}-(C=O)-R_{32}, -(C=S), -(C=S)-C_{1-6}alkyl, -(C=S)-C_{2-6}alkenyl, -(C=S)-O-C_{1-6}alkyl, -(C=S)-Het_6, -(C=S)-Ar_6, -(C=S)-C_{3-6}cycloalkyl, -(C=S)-$NR_{31}R_{32}$, -(C=S)-NR_{31}-(C=S)-R_{32}, -Het_6, -Ar_6, and -C_{3-6}cycloalkyl;

wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from =O, –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Het_6, -Ar_6, -$NR_{25}R_{26}$, -(C=O)-$NR_{25}R_{26}$, -NR_{33}(C=O)-$NR_{25}R_{26}$, -(C=S)-$NR_{25}R_{26}$, and -NR_{33}(C=S)-$NR_{25}R_{26}$; and

wherein each of said -C_{3-6}cycloalkyl is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl, =O, –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_{12}, -Ar_{11}, and –$NR_{53}R_{54}$, -(C=O)-$NR_{53}R_{54}$, -NR_{55}(C=O)-$NR_{53}R_{54}$, -(C=S)-$NR_{53}R_{54}$, and -NR_{55}(C=S)-$NR_{53}R_{54}$;

R_8 is selected from –NR_{34}-(C=O)-R_{35}, –NR_{34}-(C=S)-R_{35}, -NR_{36}-(C=O)-$NR_{34}R_{35}$, -NR_{36}-(C=S)-$NR_{34}R_{35}$, -NR_{34}-(SO_2)-R_{35}, -NR_{34}-(C=O)-O-R_{35}, -NR_{34}-(C=S)-O-R_{35}, -O-(C=O)-$NR_{34}R_{35}$, and -O-(C=S)-$NR_{34}R_{35}$;

R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, R_{29}, R_{30}, R_{31}, R_{32}, R_{33}, R_{34}, R_{35}, R_{36}, R_{37}, R_{38}, R_{39}, R_{40}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, R_{49}, R_{50}, R_{53}, R_{54} and R_{55} are each independently selected from –H, -halo, =O, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Ar_5 and –Het_7; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Het_7, -Ar_5 and –$NR_{51}R_{52}$;

R_{51} and R_{52} are each independently selected from –H, -halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Ar_{10} and –Het_{10};

R_{42} is selected from -H, -OH, -halo, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -$NR_{46}R_{47}$, -C_{3-6}cycloalkyl, -Ar_9 and -Het_8;

R_{43} is selected from –H -C_{1-6}alkyl, and -C_{3-6}cycloalkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_5, -C_{3-6}cycloalkyl –Ar_4, and –$NR_{44}R_{45}$;

A is selected from -$(CH_2)_n$-Y-$(CH_2)_m$-, –(C=O)-, –(C=S)-, -(C=N)-R_{49}-, -(SO_2)-, -SO_2-NR_5-, -(C=O)-NR_5-, -(C=S)-NR_5-, -NR_5-(C=O)-NR_7-, -NR_5-(C=S)-NR_7-, -NR_6,-, -NR_5-(C=O)-O-, -NR_5-(C=S)-O-, and -CHR_8-;

X_1 is selected from –C_{1-6}alkyl-, –O-C_{1-6}alkyl-, –S-C_{1-6}alkyl-, -(C=O)-, -NR_3-(C=O)-, -C_{1-6}alkyl-NR_3-, -NR_3-, -(C=O)-, -NR_3-(C=O)-NR_{48}-, -NR_3-C_{1-6}alkyl-, -NR_3-SO_2-, -NR_3-(C=O)-C_{1-6}alkyl-, -(C=O)-NR_3-C_{1-6}alkyl-, –O-C_{1-6}alkyl-O-C_{1-6}alkyl- and -C_{1-6}alkyl-NR_3-C_{1-6}alkyl-; wherein each of said -C_{1-6}alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -phenyl, and -$NR_{37}R_{38}$;

X_2 is selected from –C_{1-6}alkyl-, –O-C_{1-6}alkyl-, –S-C_{1-6}alkyl-, -(C=O)-, -NR_2-(C=O)-, -C_{1-6}alkyl-NR_2-, -NR_2-, -(C=O)-, -NR_2-(C=O)-NR_{50}-, -NR_2-C_{1-6}alkyl-, -NR_2-SO_2-, -NR_2-(C=O)-C_{1-6}alkyl-, -(C=O)-NR_2-C_{1-6}alkyl-, –O-C_{1-6}alkyl-O-C_{1-6}alkyl- and -C_{1-6}alkyl-NR_2-C_{1-6}alkyl-; wherein each of said

-C_{1-6}alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -phenyl and -$NR_{39}R_{40}$;

Y is selected from a direct bond, -CHR_{42}-, -O-, -S-, and –NR_{43}-;

Ar_1, Ar_2, Ar_3, Ar_4, Ar_5, Ar_6, Ar_7, Ar_8, Ar_9, Ar_{10} and Ar_{11} are each independently a 5- to 10-membered aromatic heterocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of said Ar_1, Ar_2, Ar_3, Ar_4, Ar_5, Ar_6, Ar_7, Ar_8, Ar_9, and Ar_{10} being optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, and –$NR_{19}R_{20}$; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 -halo;

Het_1, Het_2, Het_3, Het_4, Het_5, Het_6, Het_7, Het_8, Het_9, Het_{10}, and Het_{12} are each independently a 4- to 10-membered heterocycle having from 1 to 3 heteroatoms selected from O, N and S, wherein each of said Het_1, Het_2, Het_3, Het_4, Het_5, Het_6, Het_7, Het_8, Het_9, Het_{10}, and Het_{12} is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, –C_{1-6}alkyl, -OC_{1-6}alkyl, -SC_{1-6}alkyl, =O, -(C=O)-C_{1-6}alkyl, and -$NR_{21}R_{22}$; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 -halo;

Z_1, Z_2, Z_3, Z_4 and Z_5 are each independently selected from C and N; and

m and n are each independently 1, 2, 3, or 4;

for use in the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease.

2. A compound of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, wherein

A_1 is C and A_2 is N;

R_1 and R_{41} are each independently selected from –H, –halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -NR_9R_{10}, -(C=O)-R_4, -(C=S)-R_4, -SO_2-R_4, -CN, -NR_9-SO_2-R_4, -C_{3-6}cycloalkyl, -Ar_7 and –Het_1; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, -$NR_{11}R_{12}$, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;

R_2 is selected from –H, -halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -(C=O)-C_{1-6}alkyl, -(C=S)-C_{1-6}alkyl, -(C=O)-O-C_{1-6}alkyl, -(C=S)-O-C_{1-6}alkyl, -(C=O)-$NR_{27}R_{28}$, -(C=S)-$NR_{27}R_{28}$, -C_{3-6}cycloalkyl, -Het_3, -Ar_2, -(C=O)-Het_3, -(C=S)-Het_3, -(C=O)-Ar_2, -(C=S)-Ar_2, -(C=O)-C_{3-6}cycloalkyl, -(C=S)-C_{3-6}cycloalkyl, and -SO_2-C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_3, -Ar_2, and -$NR_{13}R_{14}$;

R_3 is selected from –H, -halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -(C=O)-C_{1-6}alkyl, -(C=S)-C_{1-6}alkyl, -(C=O)-O-C_{1-6}alkyl, -(C=S)-O-C_{1-6}alkyl, -(C=O)-$NR_{29}R_{30}$, -(C=S)-$NR_{29}R_{30}$, -C_{3-6}cycloalkyl -Het_2, -Ar_3, -(C=O)-Het_2, -(C=S)-Het_2, -(C=O)-Ar_3, -(C=S)-Ar_3, -(C=O)-C_{3-6}cycloalkyl, -(C=S)-C_{3-6}cycloalkyl and -SO_2-C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Het_2, -Ar_3, and -$NR_{15}R_{16}$;

R_4 is independently selected from –halo, –OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -$NR_{17}R_{18}$, -C_{3-6}cycloalkyl, -Ar_8 and -Het_4;

R_5 and R_7 are each independently selected from –H, -OH, -halo, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_9, -Ar_1, -C_{3-6}cycloalkyl, -SO_2-Ar_1, -SO_2, -SO_2-C_{1-6}alkyl, -(C=O), -(C=O)-C_{1-6}alkyl, -(C=S), -(C=S)-C_{1-6}alkyl, -O-(C=O)-C_{1-6}alkyl, -O-(C=S)-C_{1-6}alkyl, -(C=O)-O-C_{1-6}alkyl, and -(C=S)-O-C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Ar_1, -Het_9, and -$NR_{23}R_{24}$;

R_6 is selected from -C_{1-6}alkyl, -SO_2, -SO_2-C_{1-6}alkyl, -SO_2-C_{3-6}cycloalkyl, -(C=O), -(C=O)-C_{1-6}alkyl, -(C=O)-C_{2-6}alkenyl, -(C=O)-O-C_{1-6}alkyl, -(C=O)-Het_6, -(C=O)-Ar_6, -(C=O)-C_{3-6}cycloalkyl, -(C=O)-$NR_{31}R_{32}$, -(C=O)-NR_{31}-(C=O)-R_{32}, -(C=S), -(C=S)-C_{1-6}alkyl, -(C=S)-C_{2-6}alkenyl, -(C=S)-O-C_{1-6}alkyl, -(C=S)-Het_6, -(C=S)-Ar_6, -(C=S)-C_{3-6}cycloalkyl, -(C=S)-$NR_{31}R_{32}$, -(C=S)-NR_{31}-(C=S)-R_{32}, -Het_6, -Ar_6, and -C_{3-6}cycloalkyl;

wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from =O, –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Het_6, -Ar_6, -$NR_{25}R_{26}$, -(C=O)-$NR_{25}R_{26}$, -NR_{33}(C=O)-$NR_{25}R_{26}$, -(C=S)-$NR_{25}R_{26}$, and -NR_{33}(C=S)-$NR_{25}R_{26}$; and

wherein each of said -C_{3-6}cycloalkyl is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl, =O, –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_{12}, -Ar_{11}, and –$NR_{53}R_{54}$, -(C=O)-$NR_{53}R_{54}$, -NR_{55}(C=O)-$NR_{53}R_{54}$, -(C=S)-$NR_{53}R_{54}$, and -NR_{55}(C=S)-$NR_{53}R_{54}$;

R_8 is selected from –NR_{34}-(C=O)-R_{35}, –NR_{34}-(C=S)-R_{35}, -NR_{36}-(C=O)-$NR_{34}R_{35}$, -NR_{36}-(C=S)-$NR_{34}R_{35}$, -NR_{34}-(SO_2)-R_{35}, -NR_{34}-(C=O)-O-R_{35}, -NR_{34}-(C=S)-O-R_{35}, -O-(C=O)-$NR_{34}R_{35}$, and -O-(C=S)-$NR_{34}R_{35}$;

R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, R_{29}, R_{30}, R_{31}, R_{32}, R_{33}, R_{34}, R_{35}, R_{36}, R_{37}, R_{38}, R_{39}, R_{40}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, R_{49}, R_{50}, R_{53}, R_{54} and R_{55} are each independently selected from –H, -halo, =O, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Ar_5 and –Het_7; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Het_7, -Ar_5 and –$NR_{51}R_{52}$;

R_{51} and R_{52} are each independently selected from –H, -halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Ar_{10} and –Het_{10};

R_{42} is selected from -H, -OH, -halo, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -$NR_{46}R_{47}$, -C_{3-6}cycloalkyl, -Ar_9 and -Het_8;

R_{43} is selected from –H -C_{1-6}alkyl, and -C_{3-6}cycloalkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_5, -C_{3-6}cycloalkyl –Ar_4, and –$NR_{44}R_{45}$;

A is selected from -$(CH_2)_n$-Y-$(CH_2)_m$-, –(C=O)-, –(C=S)-, -(C=N)-R_{49}-, -(SO_2)-, -SO_2-NR_5-, -(C=O)-NR_5-, -(C=S)-NR_5-, -NR_5-(C=O)-NR_7-, -NR_5-(C=S)-NR_7-, -NR_6,-, -NR_5-(C=O)-O-, -NR_5-(C=S)-O-, and -CHR_8-;

X_1 is selected from $-C_{1-6}$alkyl-, $-O-C_{1-6}$alkyl-, $-S-C_{1-6}$alkyl-, -(C=O)-, $-NR_3-(C=O)-$, $-C_{1-6}$alkyl-NR_3-, $-NR_3-$, -(C=O)-, $-NR_3-(C=O)-NR_{48}-$, $-NR_3-C_{1-6}$alkyl-, $-NR_3-SO_2-$, $-NR_3-(C=O)-C_{1-6}$alkyl-, -(C=O)-NR_3-C_{1-6}alkyl-, $-O-C_{1-6}$alkyl-O-C_{1-6}alkyl- and $-C_{1-6}$alkyl-NR_3-C_{1-6}alkyl-; wherein each of said $-C_{1-6}$alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, $-C_{1-6}$alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -phenyl, and $-NR_{37}R_{38}$;

X_2 is selected from $-C_{1-6}$alkyl-, $-O-C_{1-6}$alkyl-, $-S-C_{1-6}$alkyl-, -(C=O)-, $-NR_2-(C=O)-$, $-C_{1-6}$alkyl-NR_2-, $-NR_2-$, -(C=O)-, $-NR_2-(C=O)-NR_{50}-$, $-NR_2-C_{1-6}$alkyl-, $-NR_2-SO_2-$, $-NR_2-(C=O)-C_{1-6}$alkyl-, -(C=O)-NR_2-C_{1-6}alkyl-, $-O-C_{1-6}$alkyl-O-C_{1-6}alkyl- and $-C_{1-6}$alkyl-NR_2-C_{1-6}alkyl-; wherein each of said $-C_{1-6}$alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, $-C_{1-6}$alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -phenyl and $-NR_{39}R_{40}$;

Y is selected from a direct bond, $-CHR_{42}-$, -O-, -S-, and $-NR_{43}-$;

Ar_1, Ar_2, Ar_3, Ar_4, Ar_5, Ar_6, Ar_7, Ar_8, Ar_9, Ar_{10} and Ar_{11} are each independently a 5- to 10-membered aromatic heterocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of said Ar_1, Ar_2, Ar_3, Ar_4, Ar_5, Ar_6, Ar_7, Ar_8, Ar_9, and Ar_{10} being optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, $-C_{1-6}$alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, and $-NR_{19}R_{20}$; wherein each of said $-C_{1-6}$alkyl is optionally and independently substituted with from 1 to 3 -halo;

Het_1, Het_2, Het_3, Het_4, Het_5, Het_6, Het_7, Het_8, Het_9, Het_{10}, and Het_{12} are each independently a 4- to 10-membered heterocycle having from 1 to 3 heteroatoms selected from O, N and S, wherein each of said Het_1, Het_2, Het_3, Het_4, Het_5, Het_6, Het_7, Het_8, Het_9, Het_{10}, and Het_{12} is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, $-C_{1-6}$alkyl, -OC_{1-6}alkyl, -SC_{1-6}alkyl, =O, -(C=O)-C_{1-6}alkyl, and $-NR_{21}R_{22}$; wherein each of said $-C_{1-6}$alkyl is optionally and independently substituted with from 1 to 3 -halo;

Z_1, Z_2, Z_3, Z_4 and Z_5 are each independently selected from C and N; and

m and n are each independently 1, 2, 3, or 4;

for use in the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease.

3. A compound of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof, wherein

A_1 is N and A_2 is C

R_1 and R_{41} are each independently selected from –H, –halo, -OH, $-C_{1-6}$alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, $-NR_9R_{10}$, -(C=O)-R_4, -(C=S)-R_4, $-SO_2-R_4$, -CN, $-NR_9-SO_2-R_4$, $-C_{3-6}$cycloalkyl, $-Ar_7$ and $-Het_1$; wherein each of said $-C_{1-6}$alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, $-NR_{11}R_{12}$, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;

R_2 is selected from –H, -halo, -OH, $-C_{1-6}$alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -(C=O)-C_{1-6}alkyl, -(C=S)-C_{1-6}alkyl, -(C=O)-O-C_{1-6}alkyl, -(C=S)-O-C_{1-6}alkyl, -(C=O)-$NR_{27}R_{28}$, -(C=S)-$NR_{27}R_{28}$, $-C_{3-6}$cycloalkyl, $-Het_3$, $-Ar_2$, -(C=O)-Het_3, -(C=S)-Het_3, -(C=O)-Ar_2, -(C=S)-Ar_2, -(C=O)-C_{3-6}cycloalkyl, -(C=S)-C_{3-6}cycloalkyl, and $-SO_2-C_{1-6}$alkyl; wherein each of said $-C_{1-6}$alkyl is optionally and independently

substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_3, -Ar_2, and -$NR_{13}R_{14}$;

R_3 is selected from –H, -halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -(C=O)-C_{1-6}alkyl, -(C=S)-C_{1-6}alkyl, -(C=O)-O-C_{1-6}alkyl, -(C=S)-O-C_{1-6}alkyl, -(C=O)-$NR_{29}R_{30}$, -(C=S)-$NR_{29}R_{30}$, -C_{3-6}cycloalkyl -Het_2, -Ar_3, -(C=O)-Het_2, -(C=S)-Het_2, -(C=O)-Ar_3, -(C=S)-Ar_3, -(C=O)-C_{3-6}cycloalkyl, -(C=S)-C_{3-6}cycloalkyl and -SO_2-C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Het_2, -Ar_3, and -$NR_{15}R_{16}$;

R_4 is independently selected from –halo, –OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -$NR_{17}R_{18}$, -C_{3-6}cycloalkyl, -Ar_8 and -Het_4;

R_5 and R_7 are each independently selected from –H, -OH, -halo, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_9, -Ar_1, -C_{3-6}cycloalkyl, -SO_2-Ar_1, -SO_2, -SO_2-C_{1-6}alkyl, -(C=O), -(C=O)-C_{1-6}alkyl, -(C=S), -(C=S)-C_{1-6}alkyl, -O-(C=O)-C_{1-6}alkyl, -O-(C=S)-C_{1-6}alkyl, -(C=O)-O-C_{1-6}alkyl, and -(C=S)-O-C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Ar_1, -Het_9, and -$NR_{23}R_{24}$;

R_6 is selected from -C_{1-6}alkyl, -SO_2, -SO_2-C_{1-6}alkyl, -SO_2-C_{3-6}cycloalkyl, -(C=O), -(C=O)-C_{1-6}alkyl, -(C=O)-C_{2-6}alkenyl, -(C=O)-O-C_{1-6}alkyl, -(C=O)-Het_6, -(C=O)-Ar_6, -(C=O)-C_{3-6}cycloalkyl, -(C=O)-$NR_{31}R_{32}$, -(C=O)-NR_{31}-(C=O)-R_{32}, -(C=S), -(C=S)-C_{1-6}alkyl, -(C=S)-C_{2-6}alkenyl, -(C=S)-O-C_{1-6}alkyl, -(C=S)-Het_6, -(C=S)-Ar_6, -(C=S)-C_{3-6}cycloalkyl, -(C=S)-$NR_{31}R_{32}$, -(C=S)-NR_{31}-(C=S)-R_{32}, -Het_6, -Ar_6, and -C_{3-6}cycloalkyl;

wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from =O, –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Het_6, -Ar_6, -$NR_{25}R_{26}$, -(C=O)-$NR_{25}R_{26}$, -NR_{33}(C=O)-$NR_{25}R_{26}$, -(C=S)-$NR_{25}R_{26}$, and -NR_{33}(C=S)-$NR_{25}R_{26}$; and

wherein each of said -C_{3-6}cycloalkyl is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl, =O, –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_{12}, -Ar_{11}, and –$NR_{53}R_{54}$, -(C=O)-$NR_{53}R_{54}$, -NR_{55}(C=O)-$NR_{53}R_{54}$, -(C=S)-$NR_{53}R_{54}$, and -NR_{55}(C=S)-$NR_{53}R_{54}$;

R_8 is selected from –NR_{34}-(C=O)-R_{35}, –NR_{34}-(C=S)-R_{35}, -NR_{36}-(C=O)-$NR_{34}R_{35}$, -NR_{36}-(C=S)-$NR_{34}R_{35}$, -NR_{34}-(SO_2)-R_{35}, -NR_{34}-(C=O)-O-R_{35}, -NR_{34}-(C=S)-O-R_{35}, -O-(C=O)-$NR_{34}R_{35}$, and -O-(C=S)-$NR_{34}R_{35}$;

R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, R_{29}, R_{30}, R_{31}, R_{32}, R_{33}, R_{34}, R_{35}, R_{36}, R_{37}, R_{38}, R_{39}, R_{40}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, R_{49}, R_{50}, R_{53}, R_{54} and R_{55} are each independently selected from –H, -halo, =O, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Ar_5 and –Het_7; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Het_7, -Ar_5 and –$NR_{51}R_{52}$;

R_{51} and R_{52} are each independently selected from –H, -halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-6}cycloalkyl, -Ar_{10} and –Het_{10};

R_{42} is selected from -H, -OH, -halo, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -$NR_{46}R_{47}$, -C_{3-6}cycloalkyl, -Ar_9 and -Het_8;

R_{43} is selected from –H -C_{1-6}alkyl, and -C_{3-6}cycloalkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from –halo, –OH, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -Het_5, -C_{3-6}cycloalkyl –Ar_4, and –$NR_{44}R_{45}$;

A is selected from -$(CH_2)_n$-Y-$(CH_2)_m$-, –(C=O)-, –(C=S)-, -(C=N)-R_{49}-, -(SO_2)-, -SO_2-NR_5-, -(C=O)-NR_5-, -(C=S)-NR_5-, -NR_5-(C=O)-NR_7-, -NR_5-(C=S)-NR_7-, -NR_6,-, -NR_5-(C=O)-O-, -NR_5-(C=S)-O-, and -CHR_8- ;

X_1 is selected from –C_{1-6}alkyl-, –O-C_{1-6}alkyl-, –S-C_{1-6}alkyl-, -(C=O)-, -NR_3-(C=O)-, -C_{1-6}alkyl-NR_3-, -NR_3-, -(C=O)-, -NR_3-(C=O)-NR_{48}-, -NR_3-C_{1-6}alkyl-, -NR_3-SO_2-, -NR_3-(C=O)-C_{1-6}alkyl-, -(C=O)-NR_3-C_{1-6}alkyl-, –O-C_{1-6}alkyl-O-C_{1-6}alkyl- and -C_{1-6}alkyl-NR_3-C_{1-6}alkyl-; wherein each of said -C_{1-6}alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -phenyl, and -$NR_{37}R_{38}$;

X_2 is selected from –C_{1-6}alkyl-, –O-C_{1-6}alkyl-, –S-C_{1-6}alkyl-, -(C=O)-, -NR_2-(C=O)-, -C_{1-6}alkyl-NR_2-, -NR_2-, -(C=O)-, -NR_2-(C=O)-NR_{50}-, -NR_2-C_{1-6}alkyl-, -NR_2-SO_2-, -NR_2-(C=O)-C_{1-6}alkyl-, -(C=O)-NR_2-C_{1-6}alkyl-, –O-C_{1-6}alkyl-O-C_{1-6}alkyl- and -C_{1-6}alkyl-NR_2-C_{1-6}alkyl-; wherein each of said -C_{1-6}alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -phenyl and -$NR_{39}R_{40}$;

Y is selected from a direct bond, -CHR_{42}-, -O-, -S-, and –NR_{43}-;

Ar_1, Ar_2, Ar_3, Ar_4, Ar_5, Ar_6, Ar_7, Ar_8, Ar_9, Ar_{10} and Ar_{11} are each independently a 5- to 10-membered aromatic heterocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of said Ar_1, Ar_2, Ar_3, Ar_4, Ar_5, Ar_6, Ar_7, Ar_8, Ar_9, and Ar_{10} being optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, and –$NR_{19}R_{20}$; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 -halo;

Het_1, Het_2, Het_3, Het_4, Het_5, Het_6, Het_7, Het_8, Het_9, Het_{10}, and Het_{12} are each independently a 4- to 10-membered heterocycle having from 1 to 3 heteroatoms selected from O, N and S, wherein each of said Het_1, Het_2, Het_3, Het_4, Het_5, Het_6, Het_7, Het_8, Het_9, Het_{10}, and Het_{12} is optionally and independently substituted with from 1 to 3 substituents selected from –halo, -OH, –C_{1-6}alkyl, -OC_{1-6}alkyl, -SC_{1-6}alkyl, =O, -(C=O)-C_{1-6}alkyl, and -$NR_{21}R_{22}$; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 -halo;

Z_1, Z_2, Z_3, Z_4 and Z_5 are each independently selected from C and N; and

m and n are each independently 1, 2, 3, or 4;

for use in the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease.

4. A compound of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof,

Wherein

A_1 and A_2 are selected from C and N; wherein when A_1 is C, then A_2 is N; and wherein when A_2 is C, then A_1 is N;

R_1 and R_{41} are each independently selected from –H, –halo, -C_{1-6}alkyl, -(C=O)-R_4, and -CN; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -O-C_{1-6}alkyl;

R_2 is selected from –H, and -C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with -$NR_{13}R_{14}$;

R_3 is selected from –H, and -C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with -$NR_{15}R_{16}$;

R_4 is -$NR_{17}R_{18}$;

R_5 is –H;

R_6 is selected from -C_{1-6}alkyl, -(C=O)-C_{1-6}alkyl, -(C=O)-C_{3-6}cycloalkyl, -Het_6, and -C_{3-6}cycloalkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -O-C_{1-6}alkyl and -Het_6;

and wherein each of said -C_{3-6}cycloalkyl is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl;

R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, are each independently selected from –H, and -C_{1-6}alkyl;

R_{43} is selected from –H, and -C_{1-6}alkyl;

A is selected from -$(CH_2)_n$-Y-$(CH_2)_m$-, -NR_6-, and -(C=O)-NR_5- ;

X_1 is selected from –O-C_{1-6}alkyl-, -C_{1-6}alkyl-NR_3-, and -C_{1-6}alkyl-NR_3-C_{1-6}alkyl-; wherein each of said -C_{1-6}alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl;

X_2 is selected from –O-C_{1-6}alkyl-, -C_{1-6}alkyl-NR_2-; wherein each of said -C_{1-6}alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl;

Y is –NR_{43}-;

Het_6 is a 4- to 10-membered heterocycle having from 1 to 3 heteroatoms selected from O, N and S;

Z_1, Z_2, Z_3, Z_4 and Z_5 are each independently selected from C and N; and

m and n are each independently 1, 2, 3, or 4;

for use in the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease.

5. A compound of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof,

Wherein

A_1 is C and A_2 is N;

R_1 and R_{41} are each independently selected from –H, –halo, -C_{1-6}alkyl, -(C=O)-R_4, and -CN; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -O-C_{1-6}alkyl;

R_2 is selected from –H, and -C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with -$NR_{13}R_{14}$;

R_3 is selected from –H, and -C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with -$NR_{15}R_{16}$;

R_4 is -$NR_{17}R_{18}$;

R_5 is –H;

R_6 is selected from -C_{1-6}alkyl, -(C=O)-C_{1-6}alkyl, -(C=O)-C_{3-6}cycloalkyl, -Het_6, and -C_{3-6}cycloalkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -O-C_{1-6}alkyl and -Het_6;
and wherein each of said -C_{3-6}cycloalkyl is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl;

R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, are each independently selected from –H, and -C_{1-6}alkyl;

R_{43} is selected from –H, and -C_{1-6}alkyl;

A is selected from -$(CH_2)_n$-Y-$(CH_2)_m$-, -NR_6-, and -(C=O)-NR_5-;

X_1 is selected from –O-C_{1-6}alkyl-, -C_{1-6}alkyl-NR_3-, and -C_{1-6}alkyl-NR_3-C_{1-6}alkyl-; wherein each of said -C_{1-6}alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl;

X_2 is selected from –O-C_{1-6}alkyl-, -C_{1-6}alkyl-NR_2-; wherein each of said -C_{1-6}alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl;

Y is –NR_{43}-;

Het_6 is a 4- to 10-membered heterocycle having from 1 to 3 heteroatoms selected from O, N and S;

Z_1, Z_2, Z_3, Z_4 and Z_5 are each independently selected from C and N; and

m and n are each independently 1, 2, 3, or 4;

for use in the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease.

6. A compound of Formula I or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, N-oxide form, or solvate thereof,

Wherein

A_1 is N and A_2 is C;

R_1 and R_{41} are each independently selected from –H, –halo, -C_{1-6}alkyl, -(C=O)-R_4, and -CN; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -O-C_{1-6}alkyl;

R_2 is selected from –H, and -C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with -$NR_{13}R_{14}$;

R_3 is selected from –H, and -C_{1-6}alkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with -$NR_{15}R_{16}$;

R_4 is -$NR_{17}R_{18}$;

R_5 is –H;

R_6 is selected from -C_{1-6}alkyl, -(C=O)-C_{1-6}alkyl, -(C=O)-C_{3-6}cycloalkyl, -Het_6, and -C_{3-6}cycloalkyl; wherein each of said -C_{1-6}alkyl is optionally and independently substituted with from 1 to 3 substituents selected from -O-C_{1-6}alkyl and -Het_6;
and wherein each of said -C_{3-6}cycloalkyl is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl;

R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, are each independently selected from –H, and -C_{1-6}alkyl;

R_{43} is selected from –H, and -C_{1-6}alkyl;

A is selected from -$(CH_2)_n$-Y-$(CH_2)_m$-, -NR_6-, and -(C=O)-NR_5- ;

X_1 is selected from –O-C_{1-6}alkyl-, -C_{1-6}alkyl-NR_3-, and -C_{1-6}alkyl-NR_3-C_{1-6}alkyl-; wherein each of said -C_{1-6}alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl;

X_2 is selected from –O-C_{1-6}alkyl-, -C_{1-6}alkyl-NR_2-; wherein each of said -C_{1-6}alkyl- is optionally and independently substituted with from 1 to 3 substituents selected from -C_{1-6}alkyl;

Y is –NR_{43}-;

Het_6 is a 4- to 10-membered heterocycle having from 1 to 3 heteroatoms selected from O, N and S;

Z_1, Z_2, Z_3, Z_4 and Z_5 are each independently selected from C and N; and

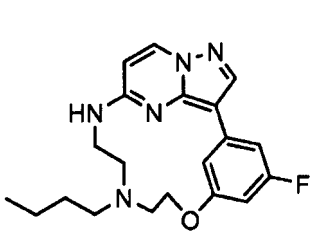
m and n are each independently 1, 2, 3, or 4;

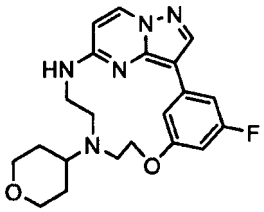
for use in the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease.

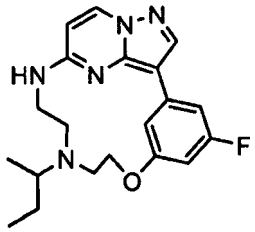
7. A compound as defined in any one of claims 1 to 6 for use in the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease; wherein the pyrazolopyrimidine or the imidazopyridazine moiety is linked to the aryl or heteroaryl moiety at position Z_4 or Z_5, in accordance with the numbering as provided in Formula I.

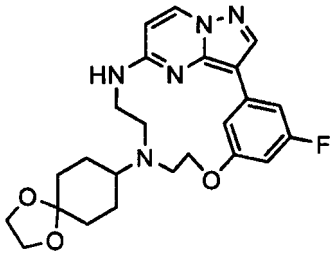
8. A compound as defined in any one of claims 1 to 6 for use in the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease; wherein R_1 is linked to the aryl or heteroaryl moiety at position Z_1, Z_2 or Z_3, in accordance with the numbering as provided in Formula I.

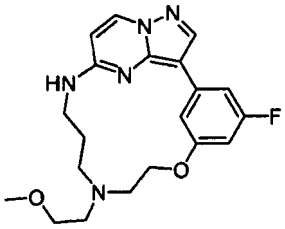
9. A compound selected from the list comprising:

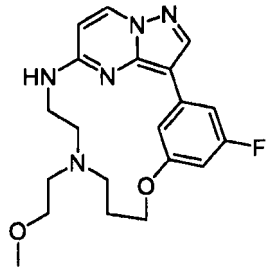


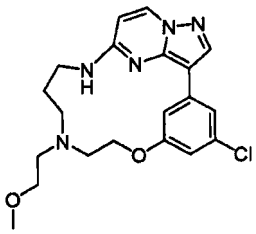


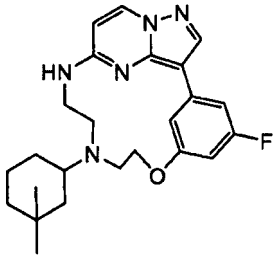


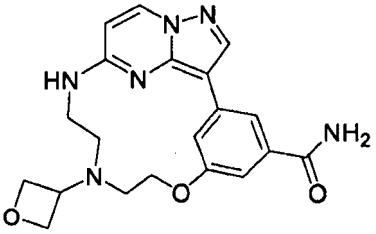


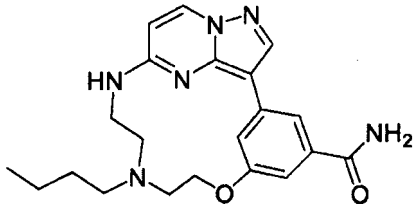


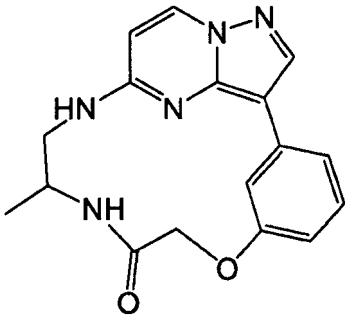


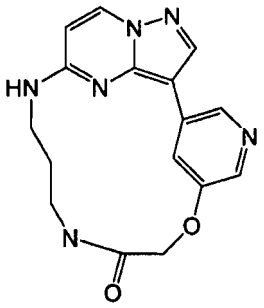


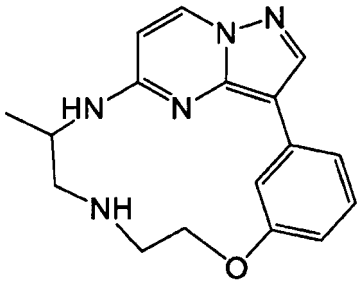












10. A compound as defined in any one of claims 1 to 9 for use in the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease; wherein the RIP2-kinase associated disease is an inflammatory disorder, in particular Crohn's disease, bowel disease, Sarcoidosis, psoriasis, rheumatoid arthritis, asthma, ulcerative colitis, lupus, uveitis, blau syndrome, granulomatous inflammation, in particular behçet's disease, multiple sclerosis and insulin-resistant type 2 diabetes.

11. A pharmaceutical composition for use in the prevention and/or treatment of a RIP2-kinase associated disease comprising a compound as defined in any one of claims 1 to 9.

12. Use of a compound as defined in any one of claims 1 to 9, or a composition as defined in claim 11, suitable for inhibiting the activity of a kinase; in particular a RIP2 kinase.

13. Use of a compound as defined in any one of claims 1 to 9, or a composition as defined in claim 11, for the diagnosis, prevention and/or treatment of a RIP2-kinase associated disease.

14. A method for the prevention and/or treatment of a RIP2-kinase associated disease; said method comprising administering to a subject in need thereof a compound according to any one of claims 1 to 9 or a composition as defined in claim 11.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/055139

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/5025 A61K31/519 A61K31/5377 C07D471/22 C07D487/18
C07D487/22 C07D498/18 C07D498/22 C07D513/18 C07D515/18
A61P29/00 A61P11/06 A61P1/00 A61P19/02 A61P17/06

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)
A61K C07D

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2013/046029 A1 (IPSEN PHARMA SAS [FR]; ONCODESIGN S A [FR]) 4 April 2013 (2013-04-04) cited in the application	12
A,P	the whole document	1-11,13, 14

X,P	WO 2013/045653 A1 (ONCODESIGN S A [FR]; BLOM PETRA MARCELLA FRANCOISE [BE]; HOFLACK JAN M) 4 April 2013 (2013-04-04) cited in the application	1-8, 11-14
A,P	the whole document, in particular compounds 4-6, 13, 21, 25, 28, 33 in table 1	9,10

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

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 April 2014	09/05/2014

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	Albrecht, Silke

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/055139

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 2004 089182 A (TAKEDA CHEMICAL INDUSTRIES LTD) 25 March 2004 (2004-03-25) paragraph [0004] - paragraph [0005] paragraph [0053]	1-14
A	WO 2013/025958 A1 (GLAXO GROUP LTD [GB]; BURY MICHAEL JONATHAN [US]; CASILLAS LINDA N [US) 21 February 2013 (2013-02-21) the whole document	1-14

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2014/055139

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013046029 A1	04-04-2013	NONE	
WO 2013045653 A1	04-04-2013	NONE	
JP 2004089182 A	25-03-2004	NONE	
WO 2013025958 A1	21-02-2013	AU 2012296411 A1	06-03-2014
		CA 2845630 A1	21-02-2013
		CO 6880068 A2	28-02-2014
		TW 201321377 A	01-06-2013
		WO 2013025958 A1	21-02-2013

(19)中华人民共和国国家知识产权局

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1304714.7 2013.03.15 GB

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WO2014/140299 EN 2014.09.18

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代理人 崔锡强

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A61K 31/5377(2006.01)
C07D 471/22(2006.01)
C07D 487/18(2006.01)
C07D 487/22(2006.01)
C07D 498/18(2006.01)
C07D 498/22(2006.01)
C07D 513/18(2006.01)
C07D 515/18(2006.01)
A61P 29/00(2006.01)
A61P 11/06(2006.01)
A61P 1/00(2006.01)
A61P 19/02(2006.01)
A61P 17/06(2006.01)

权利要求书10页 说明书52页

(54)发明名称

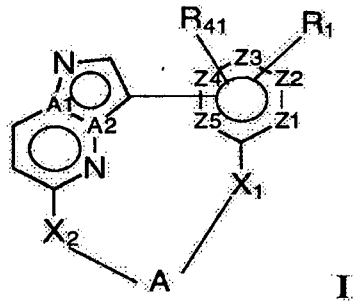
大环 RIP2 激酶抑制剂

(57)摘要

本发明涉及大环化合物和含所述化合物的组合物，其用作激酶抑制剂、特别是用作 RIP2 和/或其突变体的抑制剂，用于诊断、预防和/或治疗 RIP2-激酶相关疾病。此外，本发明提供使用所述化合物，例如作为药物或诊断剂的方法。

CN 105228625 A

1. 式 I 的化合物或其立体异构体、互变异构体、外消旋体、代谢物、前药、盐、水合物、N- 氧化物形式或溶剂化物，用于诊断、预防和 / 或治疗 RIP2- 激酶相关疾病，



I

其中

A_1和 A_2选自 C 和 N；其中当 A_1是 C 时，则 A_2是 N；且其中当 A_2是 C 时，则 A_1是 N；

R_1和 R_{41}的每个独立地选自 -H、- 卤素、-OH、$-C_{1\text{-}6}$烷基、$-O-C_{1\text{-}6}$烷基、$-S-C_{1\text{-}6}$烷基、$-NR_9R_{10}$、$-(C=O)-R_4$、$-(C=S)-R_4$、$-SO_2-R_4$、-CN、$-NR_9-SO_2-R_4$、$-C_{3\text{-}6}$环烷基、$-Ar_7$和 $-Het_1$；其中所述 $-C_{1\text{-}6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-NR_{11}R_{12}$、$-O-C_{1\text{-}6}$烷基和 $-S-C_{1\text{-}6}$烷基的取代基取代；

R_2选自 -H、- 卤素、-OH、$-C_{1\text{-}6}$烷基、$-O-C_{1\text{-}6}$烷基、$-S-C_{1\text{-}6}$烷基、$-(C=O)-C_{1\text{-}6}$烷基、$-(C=S)-C_{1\text{-}6}$烷基、$-(C=O)-O-C_{1\text{-}6}$烷基、$-(C=S)-O-C_{1\text{-}6}$烷基、$-(C=O)-NR_{27}R_{28}$、$-(C=S)-NR_{27}R_{28}$、$-C_{3\text{-}6}$环烷基、$-Het_3$、$-Ar_2$、$-(C=O)-Het_3$、$-(C=S)-Het_3$、$-(C=O)-Ar_2$、$-(C=S)-Ar_2$、$-(C=O)-C_{3\text{-}6}$环烷基、$-(C=S)-C_{3\text{-}6}$环烷基和 $-SO_2-C_{1\text{-}6}$烷基；其中所述 $-C_{1\text{-}6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-O-C_{1\text{-}6}$烷基、$-S-C_{1\text{-}6}$烷基、$-Het_3$、$-Ar_2$和 $-NR_{13}R_{14}$的取代基取代；

R_3选自 -H、- 卤素、-OH、$-C_{1\text{-}6}$烷基、$-O-C_{1\text{-}6}$烷基、$-S-C_{1\text{-}6}$烷基、$-(C=O)-C_{1\text{-}6}$烷基、$-(C=S)-C_{1\text{-}6}$烷基、$-(C=O)-O-C_{1\text{-}6}$烷基、$-(C=S)-O-C_{1\text{-}6}$烷基、$-(C=O)-NR_{29}R_{30}$、$-(C=S)-NR_{29}R_{30}$、$-C_{3\text{-}6}$环烷基、$-Het_2$、$-Ar_3$、$-(C=O)-Het_2$、$-(C=S)-Het_2$、$-(C=O)-Ar_3$、$-(C=S)-Ar_3$、$-(C=O)-C_{3\text{-}6}$环烷基、$-(C=S)-C_{3\text{-}6}$环烷基和 $-SO_2-C_{1\text{-}6}$烷基；其中所述 $-C_{1\text{-}6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-O-C_{1\text{-}6}$烷基、$-S-C_{1\text{-}6}$烷基、$-C_{3\text{-}6}$环烷基、$-Het_2$、$-Ar_3$和 $-NR_{15}R_{16}$的取代基取代；

R_4独立地选自 - 卤素、-OH、$-C_{1\text{-}6}$烷基、$-O-C_{1\text{-}6}$烷基、$-S-C_{1\text{-}6}$烷基、$-NR_{17}R_{18}$、$-C_{3\text{-}6}$环烷基、$-Ar_8$和 $-Het_4$；

R_5和 R_7的每个独立地选自 -H、-OH、- 卤素、$-C_{1\text{-}6}$烷基、$-O-C_{1\text{-}6}$烷基、$-S-C_{1\text{-}6}$烷基、$-Het_9$、$-Ar_1$、$-C_{3\text{-}6}$环烷基、$-SO_2-Ar_1$、$-SO_2$、$-SO_2-C_{1\text{-}6}$烷基、$-(C=O)$、$-(C=O)-C_{1\text{-}6}$烷基、$-(C=S)$、$-(C=S)-C_{1\text{-}6}$烷基、$-O-(C=O)-C_{1\text{-}6}$烷基、$-O-(C=S)-C_{1\text{-}6}$烷基、$-(C=O)-O-C_{1\text{-}6}$烷基和 $-(C=S)-O-C_{1\text{-}6}$烷基；其中所述 $-C_{1\text{-}6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-O-C_{1\text{-}6}$烷基、$-S-C_{1\text{-}6}$烷基、$-C_{3\text{-}6}$环烷基、$-Ar_1$、$-Het_9$和 $-NR_{23}R_{24}$的取代基取代；

R_6选自 $-C_{1\text{-}6}$烷基、$-SO_2$、$-SO_2-C_{1\text{-}6}$烷基、$-SO_2-C_{3\text{-}6}$环烷基、$-(C=O)$、$-(C=O)-C_{1\text{-}6}$烷基、$-(C=O)-C_{2\text{-}6}$烯基、$-(C=O)-O-C_{1\text{-}6}$烷基、$-(C=O)-Het_6$、$-(C=O)-Ar_6$、$-(C=O)-C_{3\text{-}6}$环烷基、$-(C=O)-NR_{31}R_{32}$、$-(C=O)-NR_{31}-(C=O)-R_{32}$、$-(C=S)$、$-(C=S)-C_{1\text{-}6}$烷基、-(C

= S)-$C_{2\ 6}$烯基、-(C = S)-O-$C_{1\ 6}$烷基、-(C = S)-Het_6、-(C = S)-Ar_6、-(C = S)-$C_{3\ 6}$环烷基、-(C = S)-$NR_{31}R_{32}$、-(C = S)-NR_{31}-(C = S)-R_{32}、-Het_6、-Ar_6和-$C_{3\ 6}$环烷基；

其中所述-$C_{1\ 6}$烷基的每个任选地和独立地被1至3个选自= O、-卤素、-OH、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、-$C_{3\ 6}$环烷基、-Het_6、-Ar_6、-$NR_{25}R_{26}$、-(C = O)-$NR_{25}R_{26}$、-NR_{33}(C = O)-$NR_{25}R_{26}$、-(C = S)-$NR_{25}R_{26}$和-NR_{33}(C = S)-$NR_{25}R_{26}$的取代基取代；且

其中所述-$C_{3\ 6}$环烷基的每个任选地和独立地被1至3个选自-$C_{1\ 6}$烷基、= O、-卤素、-OH、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、-Het_{12}、-Ar_{11}和-$NR_{53}R_{54}$、-(C = O)-$NR_{53}R_{54}$、-NR_{55}(C = O)-$NR_{53}R_{54}$、-(C = S)-$NR_{53}R_{54}$和-NR_{55}(C = S)-$NR_{53}R_{54}$的取代基取代；

R_8选自-NR_{34}-(C = O)-R_{35}、-NR_{34}-(C = S)-R_{35}、-NR_{36}-(C = O)-$NR_{34}R_{35}$、-NR_{36}-(C = S)-$NR_{34}R_{35}$、-NR_{34}-(SO_2)-R_{35}、-NR_{34}-(C = O)-O-R_{35}、-NR_{34}-(C = S)-O-R_{35}、-O-(C = O)-$NR_{34}R_{35}$和-O-(C = S)-$NR_{34}R_{35}$；

R_9、R_{10}、R_{11}、R_{12}、R_{13}、R_{14}、R_{15}、R_{16}、R_{17}、R_{18}、R_{19}、R_{20}、R_{21}、R_{22}、R_{23}、R_{24}、R_{25}、R_{26}、R_{27}、R_{28}、R_{29}、R_{30}、R_{31}、R_{32}、R_{33}、R_{34}、R_{35}、R_{36}、R_{37}、R_{38}、R_{39}、R_{40}、R_{44}、R_{45}、R_{46}、R_{47}、R_{48}、R_{49}、R_{50}、R_{53}、R_{54}和R_{55}的每个独立地选自-H、-卤素、= O、-OH、-$C_{1\ 6}$烷基、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、-$C_{3\ 6}$环烷基、-Ar_5和-Het_7；其中所述-$C_{1\ 6}$烷基的每个任选地和独立地被1至3个选自-卤素、-OH、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、-$C_{3\ 6}$环烷基、-Het_7、-Ar_5和-$NR_{51}R_{52}$的取代基取代；

R_{51}和R_{52}的每个独立地选自-H、-卤素、-OH、-$C_{1\ 6}$烷基、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、-$C_{3\ 6}$环烷基、-Ar_{10}和-Het_{10}；

R_{42}选自-H、-OH、-卤素、-$C_{1\ 6}$烷基、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、-$NR_{46}R_{47}$、-$C_{3\ 6}$环烷基、-Ar_9和-Het_8；

R_{43}选自-H、-$C_{1\ 6}$烷基和-$C_{3\ 6}$环烷基；其中所述-$C_{1\ 6}$烷基的每个任选地和独立地被1至3个选自-卤素、-OH、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、-Het_5、-$C_{3\ 6}$环烷基-Ar_4和-$NR_{44}R_{45}$的取代基取代；

A选自-$(CH_2)_n$-Y-$(CH_2)_m$-、-(C = O)-、-(C = S)-、-(C = N)-R_{49}-、-(SO_2)-、-SO_2-NR_5-、-(C = O)-NR_5-、-(C = S)-NR_5-、-NR_5-(C = O)-NR_7-、-NR_5-(C = S)-NR_7-、-NR_6-、-NR_5-(C = O)-O-、-NR_5-(C = S)-O-和-CHR_8-；

X_1选自-$C_{1\ 6}$烷基-、-O-$C_{1\ 6}$烷基-、-S-$C_{1\ 6}$烷基-、-(C = O)-、-NR_3-(C = O)-、-$C_{1\ 6}$烷基-NR_3-、-NR_3-、-(C = O)-、-NR_3-(C = O)-NR_{48}-、-NR_3-$C_{1\ 6}$烷基-、-NR_3-SO_2-、-NR_3-(C = O)-$C_{1\ 6}$烷基-、-(C = O)-NR_3-$C_{1\ 6}$烷基-、-O-$C_{1\ 6}$烷基-O-$C_{1\ 6}$烷基-和-$C_{1\ 6}$烷基-NR_3-$C_{1\ 6}$烷基-；其中所述-$C_{1\ 6}$烷基-的每个任选地和独立地被1至3个选自-卤素、-OH、-$C_{1\ 6}$烷基、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、-苯基和-$NR_{37}R_{38}$的取代基取代；

X_2选自-$C_{1\ 6}$烷基-、-O-$C_{1\ 6}$烷基-、-S-$C_{1\ 6}$烷基-、-(C = O)-、-NR_2-(C = O)-、-$C_{1\ 6}$烷基-NR_2-、-NR_2-、-(C = O)-、-NR_2-(C = O)-NR_{50}-、-NR_2-$C_{1\ 6}$烷基-、-NR_2-SO_2-、-NR_2-(C = O)-$C_{1\ 6}$烷基-、-(C = O)-NR_2-$C_{1\ 6}$烷基-、-O-$C_{1\ 6}$烷基-O-$C_{1\ 6}$烷基-和-$C_{1\ 6}$烷基-NR_2-$C_{1\ 6}$烷基-；其中所述-$C_{1\ 6}$烷基-的每个任选地和独立地被1至3个选自-卤素、-OH、-$C_{1\ 6}$烷基、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、-苯基和-$NR_{39}R_{40}$的取代基取代；

Y选自直接键、-CHR_{42}-、-O-、-S-和-NR_{43}-；

Ar_1、Ar_2、Ar_3、Ar_4、Ar_5、Ar_6、Ar_7、Ar_8、Ar_9、Ar_{10}和Ar_{11}的每个独立地是5-至10-元的芳族杂环，其任选地包含1或2个选自O、N和S的杂原子；所述Ar_1、Ar_2、Ar_3、Ar_4、Ar_5、Ar_6、

Ar_7、Ar_8、Ar_9和 Ar_{10}的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-C_{1-6}$烷基、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基和 $-NR_{19}R_{20}$的取代基取代；其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 1 至 3 个 - 卤素取代；

Het_1、Het_2、Het_3、Het_4、Het_5、Het_6、Het_7、Het_8、Het_9、Het_{10}和 Het_{12}的每个独立地是 4- 至 10- 元的杂环，其具有 1 至 3 个选自 O、N 和 S 的杂原子，其中所述 Het_1、Het_2、Het_3、Het_4、Het_5、Het_6、Het_7、Het_8、Het_9、Het_{10}和 Het_{12}的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-C_{1-6}$烷基、$-OC_{1-6}$烷基、$-SC_{1-6}$烷基、= O、$-(C=O)-C_{1-6}$烷基和 $-NR_{21}R_{22}$的取代基取代；其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 1 至 3 个 - 卤素取代；

Z_1、Z_2、Z_3、Z_4和 Z_5的每个独立地选自 C 和 N；且

m 和 n 的每个独立地是 1、2、3 或 4。

2. 式 I 的化合物或其立体异构体、互变异构体、外消旋体、代谢物、前药、盐、水合物、N- 氧化物形式或溶剂化物，用于诊断、预防和 / 或治疗 RIP2- 激酶相关疾病，其中

A_1是 C，且 A_2是 N；

R_1和 R_{41}的每个独立地选自 -H、- 卤素、-OH、$-C_{1-6}$烷基、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基、$-NR_9R_{10}$、$-(C=O)-R_4$、$-(C=S)-R_4$、$-SO_2-R_4$、-CN、$-NR_9-SO_2-R_4$、$-C_{3-6}$环烷基、$-Ar_7$和 $-Het_1$；其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-NR_{11}R_{12}$、$-O-C_{1-6}$烷基和 $-S-C_{1-6}$烷基的取代基取代；

R_2选自 -H、- 卤素、-OH、$-C_{1-6}$烷基、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基、$-(C=O)-C_{1-6}$烷基、$-(C=S)-C_{1-6}$烷基、$-(C=O)-O-C_{1-6}$烷基、$-(C=S)-O-C_{1-6}$烷基、$-(C=O)-NR_{27}R_{28}$、$-(C=S)-NR_{27}R_{28}$、$-C_{3-6}$环烷基、$-Het_3$、$-Ar_2$、$-(C=O)-Het_3$、$-(C=S)-Het_3$、$-(C=O)-Ar_2$、$-(C=S)-Ar_2$、$-(C=O)-C_{3-6}$环烷基、$-(C=S)-C_{3-6}$环烷基和 $-SO_2-C_{1-6}$烷基；其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基、$-Het_3$、$-Ar_2$和 $-NR_{13}R_{14}$的取代基取代；

R_3选自 -H、- 卤素、-OH、$-C_{1-6}$烷基、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基、$-(C=O)-C_{1-6}$烷基、$-(C=S)-C_{1-6}$烷基、$-(C=O)-O-C_{1-6}$烷基、$-(C=S)-O-C_{1-6}$烷基、$-(C=O)-NR_{29}R_{30}$、$-(C=S)-NR_{29}R_{30}$、$-C_{3-6}$环烷基、$-Het_2$、$-Ar_3$、$-(C=O)-Het_2$、$-(C=S)-Het_2$、$-(C=O)-Ar_3$、$-(C=S)-Ar_3$、$-(C=O)-C_{3-6}$环烷基、$-(C=S)-C_{3-6}$环烷基和 $-SO_2-C_{1-6}$烷基；其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基、$-C_{3-6}$环烷基、$-Het_2$、$-Ar_3$和 $-NR_{15}R_{16}$的取代基取代；

R_4独立地选自 - 卤素、-OH、$-C_{1-6}$烷基、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基、$-NR_{17}R_{18}$、$-C_{3-6}$环烷基、$-Ar_8$和 $-Het_4$；

R_5和 R_7的每个独立地选自 -H、-OH、- 卤素、$-C_{1-6}$烷基、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基、$-Het_9$、$-Ar_1$、$-C_{3-6}$环烷基、$-SO_2-Ar_1$、$-SO_2$、$-SO_2-C_{1-6}$烷基、$-(C=O)$、$-(C=O)-C_{1-6}$烷基、$-(C=S)$、$-(C=S)-C_{1-6}$烷基、$-O-(C=O)-C_{1-6}$烷基、$-O-(C=S)-C_{1-6}$烷基、$-(C=O)-O-C_{1-6}$烷基和 $-(C=S)-O-C_{1-6}$烷基；其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基、$-C_{3-6}$环烷基、$-Ar_1$、$-Het_9$和 $-NR_{23}R_{24}$的取代基取代；

R_6选自 $-C_{1-6}$烷基、$-SO_2$、$-SO_2-C_{1-6}$烷基、$-SO_2-C_{3-6}$环烷基、$-(C=O)$、$-(C=O)-C_{1-6}$烷基、$-(C=O)-C_{2-6}$烯基、$-(C=O)-O-C_{1-6}$烷基、$-(C=O)-Het_6$、$-(C=O)-Ar_6$、$-(C=O)-C_{3-6}$

环烷基、-(C = O)-$NR_{31}R_{32}$、-(C = O)-NR_{31}-(C = O)-R_{32}、-(C = S)、-(C = S)-$C_{1\ 6}$烷基、-(C = S)-$C_{2\ 6}$烯基、-(C = S)-O-$C_{1\ 6}$烷基、-(C = S)-Het_{6}、-(C = S)-Ar_{6}、-(C = S)-$C_{3\ 6}$环烷基、-(C = S)-$NR_{31}R_{32}$、-(C = S)-NR_{31}-(C = S)-R_{32}、$-Het_{6}$、$-Ar_{6}$和 -$C_{3\ 6}$环烷基；

其中所述 -$C_{1\ 6}$烷基的每个任选地和独立地被 1 至 3 个选自 = O、- 卤素、-OH、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、-$C_{3\ 6}$环烷基、$-Het_{6}$、$-Ar_{6}$、$-NR_{25}R_{26}$、-(C = O)-$NR_{25}R_{26}$、$-NR_{33}$(C = O)-$NR_{25}R_{26}$、-(C = S)-$NR_{25}R_{26}$和 -NR_{33}(C = S)-$NR_{25}R_{26}$的取代基取代；且

其中所述 -$C_{3\ 6}$环烷基的每个任选地和独立地被 1 至 3 个选自 -$C_{1\ 6}$烷基、= O、- 卤素、-OH、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、-Het_{12}、$-Ar_{11}$和 -$NR_{53}R_{54}$、-(C = O)-$NR_{53}R_{54}$、$-NR_{55}$(C = O)-$NR_{53}R_{54}$、-(C = S)-$NR_{53}R_{54}$和 -NR_{55}(C = S)-$NR_{53}R_{54}$的取代基取代；

R_{8}选自 -NR_{34}-(C = O)-R_{35}、-NR_{34}-(C = S)-R_{35}、-NR_{36}-(C = O)-$NR_{34}R_{35}$、-NR_{36}-(C = S)-$NR_{34}R_{35}$、-NR_{34}-(SO_{2})-R_{35}、-NR_{34}-(C = O)-O-R_{35}、-NR_{34}-(C = S)-O-R_{35}、-O-(C = O)-$NR_{34}R_{35}$和 -O-(C = S)-$NR_{34}R_{35}$；

R_{9}、R_{10}、R_{11}、R_{12}、R_{13}、R_{14}、R_{15}、R_{16}、R_{17}、R_{18}、R_{19}、R_{20}、R_{21}、R_{22}、R_{23}、R_{24}、R_{25}、R_{26}、R_{27}、R_{28}、R_{29}、R_{30}、R_{31}、R_{32}、R_{33}、R_{34}、R_{35}、R_{36}、R_{37}、R_{38}、R_{39}、R_{40}、R_{44}、R_{45}、R_{46}、R_{47}、R_{48}、R_{49}、R_{50}、R_{53}、R_{54}和 R_{55}的每个独立地选自 -H、- 卤素、= O、-OH、-$C_{1\ 6}$烷基、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、-$C_{3\ 6}$环烷基、$-Ar_{5}$和 $-Het_{7}$；其中所述 -$C_{1\ 6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、-$C_{3\ 6}$环烷基、$-Het_{7}$、$-Ar_{5}$和 -$NR_{51}R_{52}$的取代基取代；

R_{51}和 R_{52}的每个独立地选自 -H、- 卤素、-OH、-$C_{1\ 6}$烷基、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、-$C_{3\ 6}$环烷基、$-Ar_{10}$和 $-Het_{10}$；

R_{12}选自 -H、-OH、- 卤素、-$C_{1\ 6}$烷基、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、-$NR_{46}R_{47}$、-$C_{3\ 6}$环烷基、$-Ar_{9}$和 $-Het_{8}$；

R_{43}选自 -H、-$C_{1\ 6}$烷基和 -$C_{3\ 6}$环烷基；其中所述 -$C_{1\ 6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、$-Het_{5}$、$-C_{3\ 6}$环烷基 $-Ar_{4}$和 -$NR_{44}R_{45}$的取代基取代；

A选自 -$(CH_{2})_{n}$-Y-$(CH_{2})_{m}$-、-(C = O)-、-(C = S)-、-(C = N)-R_{49}-、-(SO_{2})-、$-SO_{2}-NR_{5}$-、-(C = O)-NR_{5}-、-(C = S)-NR_{5}-、$-NR_{5}$-(C = O)-NR_{7}-、$-NR_{5}$-(C = S)-NR_{7}-、$-NR_{6}$-、$-NR_{5}$-(C = O)-O-、$-NR_{5}$-(C = S)-O- 和 $-CHR_{8}$-；

X_{1}选自 -$C_{1\ 6}$烷基 -、-O-$C_{1\ 6}$烷基 -、-S-$C_{1\ 6}$烷基 -、-(C = O)-、-NR_{3}-(C = O)-、-$C_{1\ 6}$烷基 $-NR_{3}$-、$-NR_{3}$-、-(C = O)-、$-NR_{3}$-(C = O)-NR_{48}-、$-NR_{3}-C_{1\ 6}$烷基 -、$-NR_{3}-SO_{2}$-、$-NR_{3}$-(C = O)-$C_{1\ 6}$烷基 -、-(C = O)-$NR_{3}-C_{1\ 6}$烷基 -、-O-$C_{1\ 6}$烷基 -O-$C_{1\ 6}$烷基 - 和 -$C_{1\ 6}$烷基 -$NR_{3}-C_{1\ 6}$烷基 -；其中所述 -$C_{1\ 6}$烷基 - 的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、-$C_{1\ 6}$烷基、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、- 苯基和 -$NR_{37}R_{38}$的取代基取代；

X_{2}选自 -$C_{1\ 6}$烷基 -、-O-$C_{1\ 6}$烷基 -、-S-$C_{1\ 6}$烷基 -、-(C = O)-、-NR_{2}-(C = O)-、-$C_{1\ 6}$烷基 $-NR_{2}$-、$-NR_{2}$-、-(C = O)-、$-NR_{2}$-(C = O)-NR_{50}-、$-NR_{2}-C_{1\ 6}$烷基 -、$-NR_{2}-SO_{2}$-、$-NR_{2}$-(C = O)-$C_{1\ 6}$烷基 -、-(C = O)-$NR_{2}-C_{1\ 6}$烷基 -、-O-$C_{1\ 6}$烷基 -O-$C_{1\ 6}$烷基 - 和 -$C_{1\ 6}$烷基 -$NR_{2}-C_{1\ 6}$烷基 -；其中所述 -$C_{1\ 6}$烷基 - 的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、-$C_{1\ 6}$烷基、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、- 苯基和 -$NR_{39}R_{40}$的取代基取代；

Y 选自直接键、-CHR_{42}-、-O-、-S- 和 -NR_{43}-；

Ar_{1}、Ar_{2}、Ar_{3}、Ar_{4}、Ar_{5}、Ar_{6}、Ar_{7}、Ar_{8}、Ar_{9}、Ar_{10}和 Ar_{11}的每个独立地是 5- 至 10- 元的芳

族杂环，其任选地包含 1 或 2 个选自 O、N 和 S 的杂原子；所述 Ar_1、Ar_2、Ar_3、Ar_4、Ar_5、Ar_6、Ar_7、Ar_8、Ar_9和 Ar_{10}的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-C_{1\ 6}$烷基、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基和 $-NR_{19}R_{20}$的取代基取代；其中所述 $-C_{1\ 6}$烷基的每个任选地和独立地被 1 至 3 个 - 卤素取代；

Het_1、Het_2、Het_3、Het_4、Het_5、Het_6、Het_7、Het_8、Het_9、Het_{10}和 Het_{12}的每个独立地是 4- 至 10- 元的杂环，其具有 1 至 3 个选自 O、N 和 S 的杂原子，其中所述 Het_1、Het_2、Het_3、Het_4、Het_5、Het_6、Het_7、Het_8、Het_9、Het_{10}和 Het_{12}的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-C_{1\ 6}$烷基、$-OC_{1\ 6}$烷基、$-SC_{1\ 6}$烷基、= O、$-(C=O)-C_{1\ 6}$烷基和 $-NR_{21}R_{22}$的取代基取代；其中所述 $-C_{1\ 6}$烷基的每个任选地和独立地被 1 至 3 个 - 卤素取代；

Z_1、Z_2、Z_3、Z_4和 Z_5的每个独立地选自 C 和 N；且

m 和 n 的每个独立地是 1、2、3 或 4。

3. 式 I 的化合物或其立体异构体、互变异构体、外消旋体、代谢物、前药、盐、水合物、N- 氧化物形式或溶剂化物，用于诊断、预防和 / 或治疗 RIP2- 激酶相关疾病，其中

A_1是 N，且 A_2是 C

R_1和 R_{11}的每个独立地选自 -H、- 卤素、-OH、$-C_{1\ 6}$烷基、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-NR_9R_{10}$、$-(C=O)-R_4$、$-(C=S)-R_4$、$-SO_2-R_4$、-CN、$-NR_9-SO_2-R_4$、$-C_{3\ 6}$环烷基、$-Ar_7$和 $-Het_1$；其中所述 $-C_{1\ 6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-NR_{11}R_{12}$、$-O-C_{1\ 6}$烷基和 $-S-C_{1\ 6}$烷基的取代基取代；

R_2选自 -H、- 卤素、-OH、$-C_{1\ 6}$烷基、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-(C=O)-C_{1\ 6}$烷基、$-(C=S)-C_{1\ 6}$烷基、$-(C=O)-O-C_{1\ 6}$烷基、$-(C=S)-O-C_{1\ 6}$烷基、$-(C=O)-NR_{27}R_{28}$、$-(C=S)-NR_{27}R_{28}$、$-C_{3\ 6}$环烷基、$-Het_3$、$-Ar_2$、$-(C=O)-Het_3$、$-(C=S)-Het_3$、$-(C=O)-Ar_2$、$-(C=S)-Ar_2$、$-(C=O)-C_{3\ 6}$环烷基、$-(C=S)-C_{3\ 6}$环烷基和 $-SO_2-C_{1\ 6}$烷基；其中所述 $-C_{1\ 6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-Het_3$、$-Ar_2$和 $-NR_{13}R_{14}$的取代基取代；

R_3选自 -H、- 卤素、-OH、$-C_{1\ 6}$烷基、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-(C=O)-C_{1\ 6}$烷基、$-(C=S)-C_{1\ 6}$烷基、$-(C=O)-O-C_{1\ 6}$烷基、$-(C=S)-O-C_{1\ 6}$烷基、$-(C=O)-NR_{29}R_{30}$、$-(C=S)-NR_{29}R_{30}$、$-C_{3\ 6}$环烷基、$-Het_2$、$-Ar_3$、$-(C=O)-Het_2$、$-(C=S)-Het_2$、$-(C=O)-Ar_3$、$-(C=S)-Ar_3$、$-(C=O)-C_{3\ 6}$环烷基、$-(C=S)-C_{3\ 6}$环烷基和 $-SO_2-C_{1\ 6}$烷基；其中所述 $-C_{1\ 6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-C_{3\ 6}$环烷基、$-Het_2$、$-Ar_3$和 $-NR_{15}R_{16}$的取代基取代；

R_4独立地选自 - 卤素、-OH、$-C_{1\ 6}$烷基、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-NR_{17}R_{18}$、$-C_{3\ 6}$环烷基、$-Ar_8$和 $-Het_4$；

R_5和 R_7的每个独立地选自 -H、-OH、- 卤素、$-C_{1\ 6}$烷基、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-Het_9$、$-Ar_1$、$-C_{3\ 6}$环烷基、$-SO_2-Ar_1$、$-SO_2$、$-SO_2-C_{1\ 6}$烷基、$-(C=O)$、$-(C=O)-C_{1\ 6}$烷基、$-(C=S)$、$-(C=S)-C_{1\ 6}$烷基、$-O-(C=O)-C_{1\ 6}$烷基、$-O-(C=S)-C_{1\ 6}$烷基、$-(C=O)-O-C_{1\ 6}$烷基和 $-(C=S)-O-C_{1\ 6}$烷基；其中所述 $-C_{1\ 6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-C_{3\ 6}$环烷基、$-Ar_1$、$-Het_9$和 $-NR_{23}R_{24}$的取代基取代；

R_6选自 $-C_{1\ 6}$烷基、$-SO_2$、$-SO_2-C_{1\ 6}$烷基、$-SO_2-C_{3\ 6}$环烷基、$-(C=O)$、$-(C=O)-C_{1\ 6}$烷

基、-(C = O)-C_{2-6}烯基、-(C = O)-O-C_{1-6}烷基、-(C = O)-Het $_{6}$、-(C = O)-Ar_6、-(C = O)-C_{3-6}环烷基、-(C = O)-$NR_{31}R_{32}$、-(C = O)-NR_{31}-(C = O)-R_{32}、-(C = S)、-(C = S)-C_{1-6}烷基、-(C = S)-C_{2-6}烯基、-(C = S)-O-C_{1-6}烷基、-(C = S)-Het $_{6}$、-(C = S)-Ar_6、-(C = S)-C_{3-6}环烷基、-(C = S)-$NR_{31}R_{32}$、-(C = S)-NR_{31}-(C = S)-R_{32}、-Het_6、-Ar_6和-C_{3-6}环烷基；

其中所述-C_{1-6}烷基的每个任选地和独立地被1至3个选自=O、-卤素、-OH、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-C_{3-6}环烷基、-Het $_{6}$、-Ar_6、-$NR_{25}R_{26}$、-(C = O)-$NR_{25}R_{26}$、-NR_{33}(C = O)-$NR_{25}R_{26}$、-(C = S)-$NR_{25}R_{26}$和-NR_{33}(C = S)-$NR_{25}R_{26}$的取代基取代；且

其中所述-C_{3-6}环烷基的每个任选地和独立地被1至3个选自-C_{1-6}烷基、=O、-卤素、-OH、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-Het $_{12}$、-Ar_{11}和-$NR_{53}R_{54}$、-(C = O)-$NR_{53}R_{54}$、-NR_{55}(C = O)-$NR_{53}R_{54}$、-(C = S)-$NR_{53}R_{54}$和-NR_{55}(C = S)-$NR_{53}R_{54}$的取代基取代；

R_8选自-NR_{34}-(C = O)-R_{35}、-NR_{34}-(C = S)-R_{35}、-NR_{36}-(C = O)-$NR_{34}R_{35}$、-NR_{36}-(C = S)-$NR_{34}R_{35}$、-NR_{34}-(SO_2)-R_{35}、-NR_{34}-(C = O)-O-R_{35}、-NR_{34}-(C = S)-O-R_{35}、-O-(C = O)-$NR_{34}R_{35}$和-O-(C = S)-$NR_{34}R_{35}$；

R_9、R_{10}、R_{11}、R_{12}、R_{13}、R_{14}、R_{15}、R_{16}、R_{17}、R_{18}、R_{19}、R_{20}、R_{21}、R_{22}、R_{23}、R_{24}、R_{25}、R_{26}、R_{27}、R_{28}、R_{29}、R_{30}、R_{31}、R_{32}、R_{33}、R_{34}、R_{35}、R_{36}、R_{37}、R_{38}、R_{39}、R_{40}、R_{41}、R_{45}、R_{46}、R_{47}、R_{48}、R_{49}、R_{50}、R_{53}、R_{54}和R_{55}的每个独立地选自-H、-卤素、=O、-OH、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-C_{3-6}环烷基、-Ar_5和-Het_7；其中所述-C_{1-6}烷基的每个任选地和独立地被1至3个选自-卤素、-OH、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-C_{3-6}环烷基、-Het $_{7}$、-Ar_5和-$NR_{51}R_{52}$的取代基取代；

R_{51}和R_{52}的每个独立地选自-H、-卤素、-OH、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-C_{3-6}环烷基、-Ar_{10}和-Het $_{10}$；

R_{42}选自-H、-OH、-卤素、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-$NR_{46}R_{47}$、-C_{3-6}环烷基、-Ar_9和-Het_8；

R_{43}选自-H、-C_{1-6}烷基和-C_{3-6}环烷基；其中所述-C_{1-6}烷基的每个任选地和独立地被1至3个选自-卤素、-OH、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-Het $_{5}$、-C_{3-6}环烷基-Ar_4和-$NR_{44}R_{45}$的取代基取代；

A选自-$(CH_2)_m$-Y-$(CH_2)_m$-、-(C = O)-、-(C = S)-、-(C = N)-R_{49}-、-(SO_2)-、-SO_2-NR_5-、-(C = O)-NR_5-、-(C = S)-NR_5-、-NR_5-(C = O)-NR_7-、-NR_5-(C = S)-NR_7-、-NR_6-、-NR_5-(C = O)-O-、-NR_5-(C = S)-O-和-CHR_8-；

X_1选自-C_{1-6}烷基-、-O-C_{1-6}烷基-、-S-C_{1-6}烷基-、-(C = O)-、-NR_3-(C = O)-、-C_{1-6}烷基-NR_3-、-NR_3-、-(C = O)-、-NR_3-(C = O)-NR_{48}-、-NR_3-C_{1-6}烷基-、-NR_3-SO_2-、-NR_3-(C = O)-C_{1-6}烷基-、-(C = O)-NR_3-C_{1-6}烷基-、-O-C_{1-6}烷基-O-C_{1-6}烷基-和-C_{1-6}烷基-NR_3-C_{1-6}烷基-；其中所述-C_{1-6}烷基-的每个任选地和独立地被1至3个选自-卤素、-OH、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-苯基和-$NR_{37}R_{38}$的取代基取代；

X_2选自-C_{1-6}烷基-、-O-C_{1-6}烷基-、-S-C_{1-6}烷基-、-(C = O)-、-NR_2-(C = O)-、-C_{1-6}烷基-NR_2-、-NR_2-、-(C = O)-、-NR_2-(C = O)-NR_{50}-、-NR_2-C_{1-6}烷基-、-NR_2-SO_2-、-NR_2-(C = O)-C_{1-6}烷基-、-(C = O)-NR_2-C_{1-6}烷基-、-O-C_{1-6}烷基-O-C_{1-6}烷基-和-C_{1-6}烷基-NR_2-C_{1-6}烷基-；其中所述-C_{1-6}烷基-的每个任选地和独立地被1至3个选自-卤素、-OH、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-苯基和-$NR_{39}R_{40}$的取代基取代；

Y选自直接键、-CHR_{42}-、-O-、-S-和-NR_{43}-；

Ar_1、Ar_2、Ar_3、Ar_4、Ar_5、Ar_6、Ar_7、Ar_8、Ar_9、Ar_{10}和 Ar_{11}的每个独立地是 5- 至 10- 元的芳族杂环，其任选地包含 1 或 2 个选自 O、N 和 S 的杂原子；所述 Ar_1、Ar_2、Ar_3、Ar_4、Ar_5、Ar_6、Ar_7、Ar_8、Ar_9和 Ar_{10}的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-C_{1\text{-}6}$烷基、$-O-C_{1\text{-}6}$烷基、$-S-C_{1\text{-}6}$烷基和 $-NR_{19}R_{20}$的取代基取代；其中所述 $-C_{1\text{-}6}$烷基的每个任选地和独立地被 1 至 3 个 - 卤素取代；

Het_1、Het_2、Het_3、Het_4、Het_5、Het_6、Het_7、Het_8、Het_9、Het_{10}和 Het_{12}的每个独立地是 4- 至 10- 元的杂环，其具有 1 至 3 个选自 O、N 和 S 的杂原子，其中所述 Het_1、Het_2、Het_3、Het_4、Het_5、Het_6、Het_7、Het_8、Het_9、Het_{10}和 Het_{12}的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-C_{1\text{-}6}$烷基、$-OC_{1\text{-}6}$烷基、$-SC_{1\text{-}6}$烷基、= O、$-(C=O)-C_{1\text{-}6}$烷基和 $-NR_{21}R_{22}$的取代基取代；其中所述 $-C_{1\text{-}6}$烷基的每个任选地和独立地被 1 至 3 个 - 卤素取代；

Z_1、Z_2、Z_3、Z_4和 Z_5的每个独立地选自 C 和 N；且

m 和 n 的每个独立地是 1、2、3 或 4。

4. 式 I 的化合物或其立体异构体、互变异构体、外消旋体、代谢物、前药、盐、水合物、N- 氧化物形式或溶剂化物，用于诊断、预防和 / 或治疗 RIP2- 激酶相关疾病，

其中

A_1和 A_2选自 C 和 N；其中当 A_1是 C 时，则 A_2是 N；且其中当 A_2是 C 时，则 A_1是 N；

R_1和 R_{41}的每个独立地选自 -H、- 卤素、$-C_{1\text{-}6}$烷基、$-(C=O)-R_4$和 -CN；其中所述 $-C_{1\text{-}6}$烷基的每个任选地和独立地被 1 至 3 个选自 $-O-C_{1\text{-}6}$烷基的取代基取代；

R_2选自 -H 和 $-C_{1\text{-}6}$烷基；其中所述 $-C_{1\text{-}6}$烷基的每个任选地和独立地被 $-NR_{13}R_{14}$取代；

R_3选自 -H 和 $-C_{1\text{-}6}$烷基；其中所述 $-C_{1\text{-}6}$烷基的每个任选地和独立地被 $-NR_{15}R_{16}$取代；

R_4是 $-NR_{17}R_{18}$；

R_5是 -H；

R_6选自 $-C_{1\text{-}6}$烷基、$-(C=O)-C_{1\text{-}6}$烷基、$-(C=O)-C_{3\text{-}6}$环烷基、$-Het_6$和 $-C_{3\text{-}6}$环烷基；

其中所述 $-C_{1\text{-}6}$烷基的每个任选地和独立地被 1 至 3 个选自 $-O-C_{1\text{-}6}$烷基和 $-Het_6$的取代基取代；

且其中所述 $-C_{3\text{-}6}$环烷基的每个任选地和独立地被 1 至 3 个选自 $-C_{1\text{-}6}$烷基的取代基取代；

R_{13}、R_{14}、R_{15}、R_{16}、R_{17}、R_{18}的每个独立地选自 -H 和 $-C_{1\text{-}6}$烷基；

R_{43}选自 -H 和 $-C_{1\text{-}6}$烷基；

A 选自 $-(CH_2)_n-Y-(CH_2)_m-$、$-NR_6-$ 和 $-(C=O)-NR_5-$；

X_1选自 $-O-C_{1\text{-}6}$烷基 -、$-C_{1\text{-}6}$烷基 $-NR_3-$ 和 $-C_{1\text{-}6}$烷基 $-NR_3-C_{1\text{-}6}$烷基 -；其中所述 $-C_{1\text{-}6}$烷基 - 的每个任选地和独立地被 1 至 3 个选自 $-C_{1\text{-}6}$烷基的取代基取代；

X_2选自 $-O-C_{1\text{-}6}$烷基 -、$-C_{1\text{-}6}$烷基 $-NR_2-$；其中所述 $-C_{1\text{-}6}$烷基 - 的每个任选地和独立地被 1 至 3 个选自 $-C_{1\text{-}6}$烷基的取代基取代；

Y 是 $-NR_{43}-$；

Het_6是 4- 至 10- 元的具有 1 至 3 个选自 O、N 和 S 的杂原子的杂环；

Z_1、Z_2、Z_3、Z_4和 Z_5的每个独立地选自 C 和 N；且

m 和 n 的每个独立地是 1、2、3 或 4。

5. 式 I 的化合物或其立体异构体、互变异构体、外消旋体、代谢物、前药、盐、水合物、

N- 氧化物形式或溶剂化物，用于诊断、预防和 / 或治疗 RIP2- 激酶相关疾病，

其中

A_1是 C，且 A_2是 N；

R_1和 R_{41}的每个独立地选自 -H、- 卤素、$-C_{1-6}$烷基、-(C = O)-R_4和 -CN；其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 1 至 3 个选自 $-O-C_{1-6}$烷基的取代基取代；

R_2选自 -H 和 $-C_{1-6}$烷基；其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 $-NR_{13}R_{14}$取代；

R_3选自 -H 和 $-C_{1-6}$烷基；其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 $-NR_{15}R_{16}$取代；

R_4是 $-NR_{17}R_{18}$；

R_5是 -H；

R_6选自 $-C_{1-6}$烷基、-(C = O)-C_{1-6}烷基、-(C = O)-C_{3-6}环烷基、$-Het_6$和 $-C_{3-6}$环烷基；

其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 1 至 3 个选自 $-O-C_{1-6}$烷基和 $-Het_6$的取代基取代；

且其中所述 $-C_{3-6}$环烷基的每个任选地和独立地被 1 至 3 个选自 $-C_{1-6}$烷基的取代基取代；

R_{13}、R_{14}、R_{15}、R_{16}、R_{17}、R_{18}的每个独立地选自 -H 和 $-C_{1-6}$烷基；

R_{43}选自 -H 和 $-C_{1-6}$烷基；

A 选自 $-(CH_2)_n-Y-(CH_2)_m-$、$-NR_6-$ 和 -(C = O)-NR_5-；

X_1选自 $-O-C_{1-6}$烷基 -、$-C_{1-6}$烷基 $-NR_3-$ 和 $-C_{1-6}$烷基 $-NR_3-C_{1-6}$烷基 -；其中所述 $-C_{1-6}$烷基 - 的每个任选地和独立地被 1 至 3 个选自 $-C_{1-6}$烷基的取代基取代；

X_2选自 $-O-C_{1-6}$烷基 -、$-C_{1-6}$烷基 $-NR_2-$；其中所述 $-C_{1-6}$烷基 - 的每个任选地和独立地被 1 至 3 个选自 $-C_{1-6}$烷基的取代基取代；

Y 是 $-NR_{43}-$；

Het_6是 4- 至 10- 元的具有 1 至 3 个选自 O、N 和 S 的杂原子的杂环；

Z_1、Z_2、Z_3、Z_4和 Z_5的每个独立地选自 C 和 N；且

m 和 n 的每个独立地是 1、2、3 或 4。

6. 式 I 的化合物或其立体异构体、互变异构体、外消旋体、代谢物、前药、盐、水合物、N- 氧化物形式或溶剂化物，用于诊断、预防和 / 或治疗 RIP2- 激酶相关疾病，

其中

A_1是 N，且 A_2是 C；

R_1和 R_{41}的每个独立地选自 -H、- 卤素、$-C_{1-6}$烷基、-(C = O)-R_4和 -CN；其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 1 至 3 个选自 $-O-C_{1-6}$烷基的取代基取代；

R_2选自 -H 和 $-C_{1-6}$烷基；其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 $-NR_{13}R_{14}$取代；

R_3选自 -H 和 $-C_{1-6}$烷基；其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 $-NR_{15}R_{16}$取代；

R_4是 $-NR_{17}R_{18}$；

R_5是 -H；

R_6选自 $-C_{1-6}$烷基、-(C = O)-C_{1-6}烷基、-(C = O)-C_{3-6}环烷基、$-Het_6$和 $-C_{3-6}$环烷基；

其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 1 至 3 个选自 $-O-C_{1-6}$烷基和 $-Het_6$的取代基取代；

且其中所述 $-C_{3-6}$环烷基的每个任选地和独立地被 1 至 3 个选自 $-C_{1-6}$烷基的取代基取

代；

R_{13}、R_{14}、R_{15}、R_{16}、R_{17}、R_{18}的每个独立地选自 -H 和 $-C_{1-6}$烷基；

R_{43}选自 -H 和 $-C_{1-6}$烷基；

A 选自 $-(CH_2)_n-Y-(CH_2)_m-$、$-NR_6-$ 和 $-(C=O)-NR_5-$；

X_1选自 $-O-C_{1-6}$烷基 -、$-C_{1-6}$烷基 $-NR_3-$ 和 $-C_{1-6}$烷基 $-NR_3-C_{1-6}$烷基 -；其中所述 $-C_{1-6}$烷基 - 的每个任选地和独立地被 1 至 3 个选自 $-C_{1-6}$烷基的取代基取代；

X_2选自 $-O-C_{1-6}$烷基 -、$-C_{1-6}$烷基 $-NR_2-$；其中所述 $-C_{1-6}$烷基 - 的每个任选地和独立地被 1 至 3 个选自 $-C_{1-6}$烷基的取代基取代；

Y 是 $-NR_{43}-$；

Het_6是 4- 至 10- 元的具有 1 至 3 个选自 O、N 和 S 的杂原子的杂环；

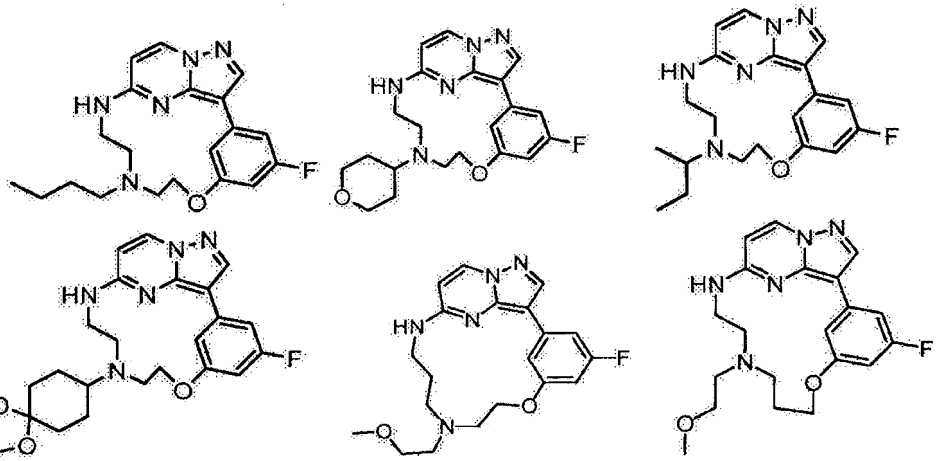
Z_1、Z_2、Z_3、Z_4和 Z_5的每个独立地选自 C 和 N；且

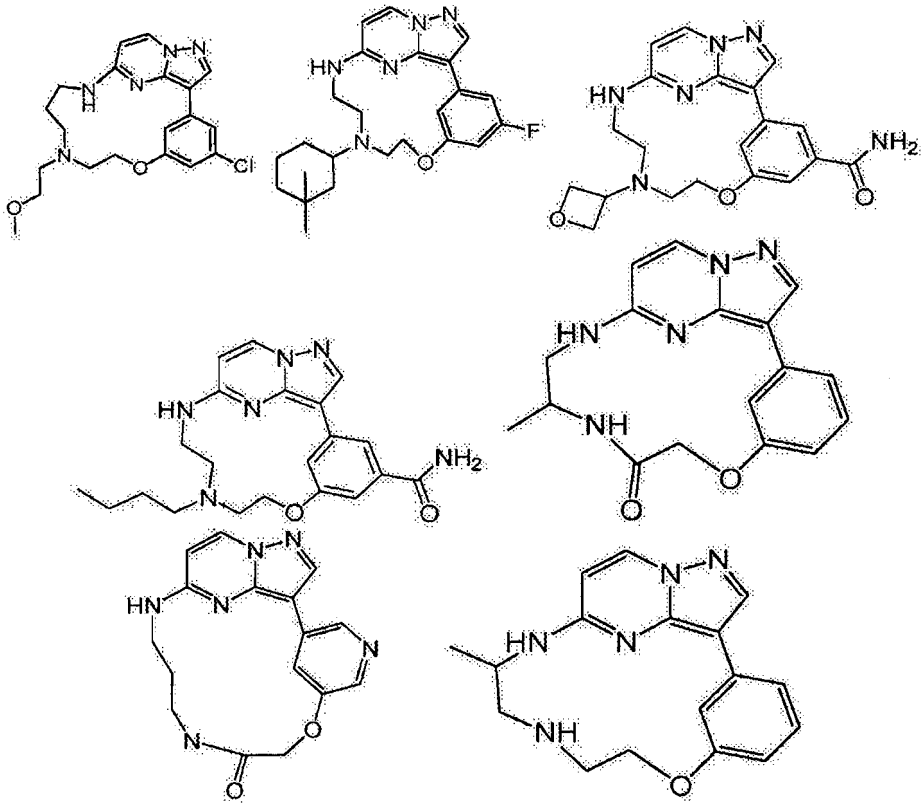
m 和 n 的每个独立地是 1、2、3 或 4。

7. 如权利要求 1 至 6 中任意一项定义的化合物，其用于诊断、预防和 / 或治疗 RIP2- 激酶相关疾病；其中吡唑并嘧啶或咪唑并哒嗪部分在 Z_4或 Z_5位连接于芳基或杂芳基部分，所述位置根据式 I 中提供的编号。

8. 如权利要求 1 至 6 中任意一项定义的化合物，其用于诊断、预防和 / 或治疗 RIP2- 激酶相关疾病；其中 R_1在 Z_1、Z_2或 Z_3位连接于芳基或杂芳基部分，所述位置根据式 I 中提供的编号。

9. 化合物，其选自：





10. 如权利要求 1 至 9 中任意一项定义的化合物，其用于诊断、预防和 / 或治疗 RIP2- 激酶相关疾病；其中所述 RIP2- 激酶相关疾病为炎性障碍、特别是克罗恩病、肠疾病、结节病、银屑病、类风湿性关节炎、哮喘、溃疡性结肠炎、狼疮、眼色素层炎、blau 综合征、肉芽肿性炎症，特别是贝赫切特病、多发性硬化和胰岛素抵抗性 2 型糖尿病。

11. 用于预防和 / 或治疗 RIP2- 激酶相关疾病的药物组合物，其包含如权利要求 1 至 9 中任意一项定义的化合物。

12. 如权利要求 1 至 9 中任意一项定义的化合物或如权利要求 11 中定义的组合物适用于抑制激酶的活性、特别是 RIP2 激酶的活性的用途。

13. 如权利要求 1 至 9 中任意一项定义的化合物或如权利要求 11 中定义的组合物在诊断、预防和 / 或治疗 RIP2- 激酶相关疾病中的用途。

14. 预防和 / 或治疗 RIP2- 激酶相关疾病的方法；所述方法包括向有需要的受试者施用根据权利要求 1 至 9 中任意一项的化合物或如权利要求 11 中定义的组合物。

大环 RIP2 激酶抑制剂

发明领域

[0001] 本发明涉及大环化合物和含所述化合物的组合物，其用作激酶抑制剂、特别是用作 RIP2 和 / 或其突变体的抑制剂，用于诊断、预防和 / 或治疗 RIP2- 激酶相关疾病。此外，本发明提供使用所述化合物，例如作为药物或诊断剂的方法。

[0002] 发明背景

[0003] 蛋白激酶构成结构相关的酶的大家族，这些酶在细胞中负责控制众多信号传导过程。已经显示它们在包括增殖、细胞代谢、细胞存活、细胞凋亡、DNA 损伤修复、细胞运动等在内的大多数细胞功能中是关键调节器。由于蛋白磷酸化缺乏控制所致的信号转导不受控制已经涉及多种疾病，包括例如癌症、炎症、变态反应、免疫疾病、CNS 障碍以及血管生成。

[0004] 在蛋白激酶家族中，一个具体的实例是包括 RIP2 的受体 - 相互作用丝氨酸 / 苏氨酸激酶。RIP2（受体相互作用蛋白 2）也被称为含 Card 的 Ice- 相关激酶 (CARDIAK)、CARD3(C- 端胱天蛋白酶募集域 3)、受体相互作用蛋白激酶 2(RIPK2) 或 Rip- 样相互作用 Clarp 激酶 (RICK)。RIP2 激酶由通过中间 (IM) 区域连接的 N- 端激酶域和 C- 端半胱天冬酶 - 募集域 (CARD) 组成 (Curr. Med. Chem. (2005) 4, 35-42))。RIP2 激酶的 CARD 域介导与其它含 CARD 的蛋白（诸如核苷酸寡聚结构域蛋白 (Nucleotide Oligomerization Domain Proteins)、NOD1 和 NOD2）间的相互作用 (J. Biol. Chem. (2000) 275, 27823-27831 及 EMBO reports(2001) 2, 736-742)。NOD1 和 NOD2 为由特定的细菌肽聚糖基元活化的细胞质受体，其在先天性免疫监视中起重要作用。在细胞内细菌暴露时，NOD1 或 NOD2 与蛋白激酶 RIP2 结合以协调 NF- κ B（核因子 κ B)- 介导的细胞因子应答。一旦与 NOD1/2 结合，RIP2 会经历 Tyr 474(Y474) 上的自磷酸化，并起分子支架功能将参与 NF- κ B 和 MAPK 活化的其他激酶 (TAK1、IKK α / β / γ) 连接在一起 (Nature Reviews Immunology(2006) 6, 9-20)。

[0005] NOD1/2 和 RIP2 均为调节 NF- κ B 的基因，且它们的活化如此引起正反馈回路，其中 NOD1/2:RIP2 的活化刺激进一步的活化和进一步的炎症。另外，多种炎症介导素激活 NOD1/2 和 RIP2 表达，包括 TNF（肿瘤坏死因子）和 IFN（干扰素）。除 NF- κ B 途径活化之外，NOD1/2:RIP2 复合物刺激自体吞噬、杀菌活性、MHC II 类的呈递和 MAPK（促分裂原活化的蛋白激酶）活化。总之，该通路调节先天免疫系统以帮助调整适当的免疫应答来消灭进犯的病原体。

[0006] RIP2- 依赖性的发信号失调已经与自身炎症性疾病相关联。NOD2 等位基因功能损失的患者容易发展为克罗恩病，一种胃肠道的炎性障碍 (Am. J. Hum. Genet. (2002) 70, 845-857 和 Microbes and Infection(2009) 11, 912-918)。与之相反，NOD2 功能增强突变体与其他炎性疾病有遗传性关联，所述炎性疾病诸如 Blau 综合征 / 早发性结节病 (EOS)、特征为眼色素层炎的儿科肉芽肿病、皮炎和关节炎 (Nature Genetics(2001) 29, 19-20 和 Current Rheumatology Reports(2005) 7, 427-433)。NOD1 中的突变体与哮喘 (Hum. Mol. Genet. (2005) 14, 935-941) 和早发性和肠外炎性肠病 (Hum. Mol. Genet. (2005) 14, 1245-1250) 有关。遗传和功能研究也已经表明 RIP2- 依赖性的发信号在多种其它肉芽肿障碍、诸如结节病 (Journal of Clinical Immunology(2009) 29, 78-89) 和

韦格纳肉芽肿 (Diagnostic Pathology(2009)4,23) 中的作用。

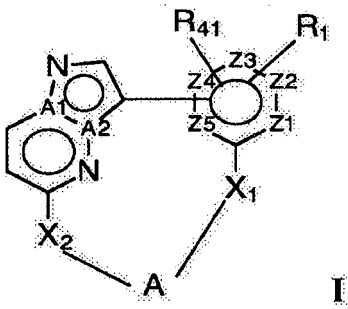
[0007] 功能损失多态性和功能增强突变体均引起炎性疾病这一事实可能是由于 NOD2 作为变阻器起作用来帮助维持正常的免疫自身稳定这一事实。炎症发信号信号途径之间缺乏协调影响炎性障碍的发展,且 NOD1/2:RIP2 活化平衡对该协调很重要。克罗恩病和结节病的治疗目前依赖于宽的、非特异性的免疫学抑制(例如,皮质类固醇)或依赖于费用和副作用显著的特异性细胞因子抑制(例如,抗-TNF 疗法)。然而,治疗不够理想,因为不是所有活性剂都同样有效,疾病在长时间范围内发生,且不是所有活性剂在同一患者中都保持有效。已显示 RIP2Y474 自身磷酸化事件对于有效的 NOD2 发信号是必需的,且其在最常见的与克罗恩病相关的功能损失的 NOD2 等位基因的存在下不发生。该自身磷酸化受非高选择性激酶抑制剂吉非替尼和厄洛替尼抑制,表明 RIP2 的酪氨酸激酶活性在炎性疾病的治疗中可以特异性地靶向 (Genes Dev. (2010)1,2666-77)。已经报道了若干临床病例,其有关吉非替尼或厄洛替尼治疗对清除银屑病或减少关节炎症状或与代谢综合征相关的胰岛素抵抗性的 2 型糖尿病有效 (The Oncologist(2013)18:e3-e5)。在建立的慢性炎性肠病的小鼠模型中,通过小分子 SB203580 对 RIP2 活性的抑制有效减少了所诱导的-结肠炎 (J Biol Chem. (2005)15,14981-14988)。然而这些小分子中没有主要和选择性地靶向 RIP2。因此本发明的目的是提供可以特异性阻断 RIP2-依赖性促炎发信号的强效的、选择性的小分子 RIP2 激酶活性抑制剂,由此在特征为增加的和/或失调的 RIP2 激酶活性的自身炎症性疾病中提供治疗益处。

[0008] 我们现已发现大环吡唑并嘧啶和咪唑并哒嗪及本发明的药学可接受的组合物可用于治疗炎性障碍、特别是克罗恩病、肠疾病、结节病、银屑病、类风湿性关节炎、哮喘和胰岛素抵抗性 2 型糖尿病、溃疡性结肠炎、狼疮、眼色素层炎、blau 综合征、肉芽肿性炎症、特别是贝赫切特病、多发性硬化和与 RIP2 激酶活性相关的疾病(即 RIP2- 激酶相关疾病)。

[0009] 发明概述

[0010] 我们已经令人惊讶地发现本文描述的大环化合物起 RIP2 激酶抑制剂作用,且因此在 RIP2- 激酶相关疾病的诊断、预防和/或治疗中非常有用。

[0011] 在第一个目的中,本发明提供了式 I 的化合物或其立体异构体、互变异构体、外消旋体、代谢物、前药 (pro-, predrug)、盐、水合物、N- 氧化物形式或溶剂化物,



I

[0012] 用于诊断、预防和/或治疗 RIP2- 激酶相关疾病,

[0013] 其中

[0014] A_1和 A_2选自 C 和 N;其中当 A_1是 C 时,则 A_2是 N;且其中当 A_2是 C 时,则 A_1是 N;

[0015] R_1和 R_{41}的每个独立地选自 -H、- 卤素、-OH、$-C_{1-6}$烷基、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷

基、$-NR_9R_{10}$、$-(C=O)-R_4$、$-(C=S)-R_4$、$-SO_2-R_4$、-CN、$-NR_9-SO_2-R_4$、$-C_{3\ 6}$环烷基、$-Ar_7$和$-Het_1$；其中所述$-C_{1\ 6}$烷基的每个任选地和独立地被1至3个选自-卤素、-OH、$-NR_{11}R_{12}$、$-O-C_{1\ 6}$烷基和$-S-C_{1\ 6}$烷基的取代基取代；

[0016] R_2选自-H、-卤素、-OH、$-C_{1\ 6}$烷基、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-(C=O)-C_{1\ 6}$烷基、$-(C=S)-C_{1\ 6}$烷基、$-(C=O)-O-C_{1\ 6}$烷基、$-(C=S)-O-C_{1\ 6}$烷基、$-(C=O)-NR_{27}R_{28}$、$-(C=S)-NR_{27}R_{28}$、$-C_{3\ 6}$环烷基、$-Het_3$、$-Ar_2$、$-(C=O)-Het_3$、$-(C=S)-Het_3$、$-(C=O)-Ar_2$、$-(C=S)-Ar_2$、$-(C=O)-C_{3\ 6}$环烷基、$-(C=S)-C_{3\ 6}$环烷基和$-SO_2-C_{1\ 6}$烷基；其中所述$-C_{1\ 6}$烷基的每个任选地和独立地被1至3个选自-卤素、-OH、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-Het_3$、$-Ar_2$和$-NR_{13}R_{14}$的取代基取代；

[0017] R_3选自-H、-卤素、-OH、$-C_{1\ 6}$烷基、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-(C=O)-C_{1\ 6}$烷基、$-(C=S)-C_{1\ 6}$烷基、$-(C=O)-O-C_{1\ 6}$烷基、$-(C=S)-O-C_{1\ 6}$烷基、$-(C=O)-NR_{29}R_{30}$、$-(C=S)-NR_{29}R_{30}$、$-C_{3\ 6}$环烷基、$-Het_2$、$-Ar_3$、$-(C=O)-Het_2$、$-(C=S)-Het_2$、$-(C=O)-Ar_3$、$-(C=S)-Ar_3$、$-(C=O)-C_{3\ 6}$环烷基、$-(C=S)-C_{3\ 6}$环烷基和$-SO_2-C_{1\ 6}$烷基；其中所述$-C_{1\ 6}$烷基的每个任选地和独立地被1至3个选自-卤素、-OH、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-C_{3\ 6}$环烷基、$-Het_2$、$-Ar_3$和$-NR_{15}R_{16}$的取代基取代；

[0018] R_4独立地选自-卤素、-OH、$-C_{1\ 6}$烷基、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-NR_{17}R_{18}$、$-C_{3\ 6}$环烷基、$-Ar_8$和$-Het_4$；

[0019] R_5和R_7的每个独立地选自-H、-OH、-卤素、$-C_{1\ 6}$烷基、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-Het_9$、$-Ar_1$、$-C_{3\ 6}$环烷基、$-SO_2-Ar_1$、$-SO_2$、$-SO_2-C_{1\ 6}$烷基、$-(C=O)$、$-(C=O)-C_{1\ 6}$烷基、$-(C=S)$、$-(C=S)-C_{1\ 6}$烷基、$-O-(C=O)-C_{1\ 6}$烷基、$-O-(C=S)-C_{1\ 6}$烷基、$-(C=O)-O-C_{1\ 6}$烷基和$-(C=S)-O-C_{1\ 6}$烷基；其中所述$-C_{1\ 6}$烷基的每个任选地和独立地被1至3个选自-卤素、-OH、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-C_{3\ 6}$环烷基、$-Ar_1$、$-Het_9$和$-NR_{23}R_{24}$的取代基取代；

[0020] R_6选自$-C_{1\ 6}$烷基、$-SO_2$、$-SO_2-C_{1\ 6}$烷基、$-SO_2-C_{3\ 6}$环烷基、$-(C=O)$、$-(C=O)-C_{1\ 6}$烷基、$-(C=O)-C_{2\ 6}$烯基、$-(C=O)-O-C_{1\ 6}$烷基、$-(C=O)-Het_6$、$-(C=O)-Ar_6$、$-(C=O)-C_{3\ 6}$环烷基、$-(C=O)-NR_{31}R_{32}$、$-(C=O)-NR_{31}-(C=O)-R_{32}$、$-(C=S)$、$-(C=S)-C_{1\ 6}$烷基、$-(C=S)-C_{2\ 6}$烯基、$-(C=S)-O-C_{1\ 6}$烷基、$-(C=S)-Het_6$、$-(C=S)-Ar_6$、$-(C=S)-C_{3\ 6}$环烷基、$-(C=S)-NR_{31}R_{32}$、$-(C=S)-NR_{31}-(C=S)-R_{32}$、$-Het_6$、$-Ar_6$和$-C_{3\ 6}$环烷基；

[0021] 其中所述$-C_{1\ 6}$烷基的每个任选地和独立地被1至3个选自=O、-卤素、-OH、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-C_{3\ 6}$环烷基、$-Het_6$、$-Ar_6$、$-NR_{25}R_{26}$、$-(C=O)-NR_{25}R_{26}$、$-NR_{33}(C=O)-NR_{25}R_{26}$、$-(C=S)-NR_{25}R_{26}$和$-NR_{33}(C=S)-NR_{25}R_{26}$的取代基取代；且

[0022] 其中所述$-C_{3\ 6}$环烷基的每个任选地和独立地被1至3个选自$-C_{1\ 6}$烷基、=O、-卤素、-OH、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-Het_{12}$、$-Ar_{11}$和$-NR_{53}R_{54}$、$-(C=O)-NR_{53}R_{54}$、$-NR_{55}(C=O)-NR_{53}R_{54}$、$-(C=S)-NR_{53}R_{54}$和$-NR_{55}(C=S)-NR_{53}R_{54}$的取代基取代；

[0023] R_8选自$-NR_{34}-(C=O)-R_{35}$、$-NR_{34}-(C=S)-R_{35}$、$-NR_{36}-(C=O)-NR_{34}R_{35}$、$-NR_{36}-(C=S)-NR_{34}R_{35}$、$-NR_{34}-(SO_2)-R_{35}$、$-NR_{34}-(C=O)-O-R_{35}$、$-NR_{34}-(C=S)-O-R_{35}$、$-O-(C=O)-NR_{34}R_{35}$和$-O-(C=S)-NR_{34}R_{35}$；

[0024] R_9、R_{10}、R_{11}、R_{12}、R_{13}、R_{14}、R_{15}、R_{16}、R_{17}、R_{18}、R_{19}、R_{20}、R_{21}、R_{22}、R_{23}、R_{24}、R_{25}、R_{26}、R_{27}、R_{28}、R_{29}、R_{30}、R_{31}、R_{32}、R_{33}、R_{34}、R_{35}、R_{36}、R_{37}、R_{38}、R_{39}、R_{40}、R_{44}、R_{45}、R_{46}、R_{47}、R_{48}、R_{49}、R_{50}、R_{53}、R_{54}和R_{55}的每个

独立地选自 -H、- 卤素、= O、-OH、$-C_{1\ 6}$烷基、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、$-C_{3\ 6}$环烷基、$-Ar_5$和 $-Het_7$;其中所述 $-C_{1\ 6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、$-C_{3\ 6}$环烷基、$-Het_{7}$、$-Ar_5$和 $-NR_{51}R_{52}$的取代基取代 ;

[0025] R_{51}和 R_{52}的每个独立地选自 -H、- 卤素、-OH、$-C_{1\ 6}$烷基、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、$-C_{3\ 6}$环烷基、$-Ar_{10}$和 $-Het_{10}$;

[0026] R_{42}选自 -H、-OH、- 卤素、$-C_{1\ 6}$烷基、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、$-NR_{46}R_{47}$、$-C_{3\ 6}$环烷基、$-Ar_9$和 $-Het_8$:

[0027] R_{43}选自 -H、$-C_{1\ 6}$烷基和 $-C_{3\ 6}$环烷基 ;其中所述 $-C_{1\ 6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、$-Het_5$、$-C_{3\ 6}$环烷基 $-Ar_4$和 $-NR_{44}R_{45}$的取代基取代 ;

[0028] A 选 自 $-(CH_2)_n-Y-(CH_2)_m-$、-(C = O)-、-(C = S)-、-(C = N)$-R_{49}$-、$-(SO_2)-$、$-SO_2-NR_5-$、-(C = O)$-NR_5-$、-(C = S)$-NR_5-$、$-NR_5-$(C = O)$-NR_7-$、$-NR_5-$(C = S)$-NR_7-$、$-NR_6-$、$-NR_5-$(C = O)-O-、$-NR_5-$(C = S)-O- 和 $-CHR_8-$;

[0029] X_1选自 $-C_{1\ 6}$烷基 -、-O-$C_{1\ 6}$烷基 -、-S-$C_{1\ 6}$烷基 -、-(C = O)-、$-NR_3-$(C = O)-、$-C_{1\ 6}$烷基 $-NR_3-$、$-NR_3-$、-(C = O)-、$-NR_3-$(C = O)$-NR_{18}-$、$-NR_3-C_{1\ 6}$烷基 -、$-NR_3-SO_2-$、$-NR_3-$(C = O)$-C_{1\ 6}$烷基 -、-(C = O)$-NR_3-C_{1\ 6}$烷基 -、-O-$C_{1\ 6}$烷基 -O-$C_{1\ 6}$烷基 - 和 $-C_{1\ 6}$烷基 $-NR_3-C_{1\ 6}$烷基 - ;其中所述 $-C_{1\ 6}$烷基 - 的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-C_{1\ 6}$烷基、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、- 苯基和 $-NR_{37}R_{38}$的取代基取代 ;

[0030] X_2选自 $-C_{1\ 6}$烷基 -、-O-$C_{1\ 6}$烷基 -、-S-$C_{1\ 6}$烷基 -、-(C = O)-、$-NR_2-$(C = O)-、$-C_{1\ 6}$烷基 $-NR_2-$、$-NR_2-$、-(C = O)-、$-NR_2-$(C = O)$-NR_{50}-$、$-NR_2-C_{1\ 6}$烷基 -、$-NR_2-SO_2-$、$-NR_2-$(C = O)$-C_{1\ 6}$烷基 -、-(C = O)$-NR_2-C_{1\ 6}$烷基 -、-O-$C_{1\ 6}$烷基 -O-$C_{1\ 6}$烷基 - 和 $-C_{1\ 6}$烷基 $-NR_2-C_{1\ 6}$烷基 - ;其中所述 $-C_{1\ 6}$烷基 - 的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-C_{1\ 6}$烷基、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、- 苯基和 $-NR_{39}R_{40}$的取代基取代 ;

[0031] Y 选自直接键、$-CHR_{42}-$、-O-、-S- 和 $-NR_{43}-$;

[0032] Ar_1、Ar_2、Ar_3、Ar_4、Ar_5、Ar_6、Ar_7、Ar_8、Ar_9、Ar_{10}和 Ar_{11}的每个独立地是 5- 至 10- 元的芳族杂环,其任选地包含 1 或 2 个选自 O、N 和 S 的杂原子 ;所述 Ar_1、Ar_2、Ar_3、Ar_4、Ar_5、Ar_6、Ar_7、Ar_8、Ar_9和 Ar_{10}的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-C_{1\ 6}$烷基、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基和 $-NR_{19}R_{20}$的取代基取代 ;其中所述 $-C_{1\ 6}$烷基的每个任选地和独立地被 1 至 3 个 - 卤素取代 ;

[0033] Het_1、Het_2、Het_3、Het_4、Het_5、Het_6、Het_7、Het_8、Het_9、Het_{10}和 Het_{12}的每个独立地是 4- 至 10- 元的杂环,其具有 1 至 3 个选自 O、N 和 S 的杂原子,其中所述 Het_1、Het_2、Het_3、Het_4、Het_5、Het_6、Het_7、Het_8、Het_9、Het_{10}和 Het_{12}的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-C_{1\ 6}$烷基、$-OC_{1\ 6}$烷基、$-SC_{1\ 6}$烷基、= O、-(C = O)$-C_{1\ 6}$烷基和 $-NR_{21}R_{22}$的取代基取代 ;其中所述 $-C_{1\ 6}$烷基的每个任选地和独立地被 1 至 3 个 - 卤素取代 ;

[0034] Z_1、Z_2、Z_3、Z_4和 Z_5的每个独立地选自 C 和 N ;且

[0035] m 和 n 的每个独立地是 1、2、3 或 4。

[0036] 在第一实施方案中,本发明提供了式 I 的化合物或其立体异构体、互变异构体、外消旋体、代谢物、前药、盐、水合物、N- 氧化物形式或溶剂化物,用于诊断、预防和 / 或治疗 RIP2- 激酶相关疾病,其中

[0037] A_1是C，且A_2是N；

[0038] R_1和R_{41}的每个独立地选自-H、-卤素、-OH、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-NR_9R_{10}、-(C=O)-R_4、-(C=S)-R_4、-SO_2-R_4、-CN、-NR_9-SO_2-R_4、-C_{3-6}环烷基、-Ar_7和-Het_1；其中所述-C_{1-6}烷基的每个任选地和独立地被1至3个选自-卤素、-OH、-$NR_{11}R_{12}$、-O-C_{1-6}烷基和-S-C_{1-6}烷基的取代基取代；

[0039] R_2选自-H、-卤素、-OH、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-(C=O)-C_{1-6}烷基、-(C=S)-C_{1-6}烷基、-(C=O)-O-C_{1-6}烷基、-(C=S)-O-C_{1-6}烷基、-(C=O)-$NR_{27}R_{28}$、-(C=S)-$NR_{27}R_{28}$、-C_{3-6}环烷基、-Het_3、-Ar_2、-(C=O)-Het_3、-(C=S)-Het_3、-(C=O)-Ar_2、-(C=S)-Ar_2、-(C=O)-C_{3-6}环烷基、-(C=S)-C_{3-6}环烷基和-SO_2-C_{1-6}烷基；其中所述-C_{1-6}烷基的每个任选地和独立地被1至3个选自-卤素、-OH、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-Het_3、-Ar_2和-$NR_{13}R_{14}$的取代基取代；

[0040] R_3选自-H、-卤素、-OH、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-(C=O)-C_{1-6}烷基、-(C=S)-C_{1-6}烷基、-(C=O)-O-C_{1-6}烷基、-(C=S)-O-C_{1-6}烷基、-(C=O)-$NR_{29}R_{30}$、-(C=S)-$NR_{29}R_{30}$、-C_{3-6}环烷基、-Het_2、-Ar_3、-(C=O)-Het_2、-(C=S)-Het_2、-(C=O)-Ar_3、-(C=S)-Ar_3、-(C=O)-C_{3-6}环烷基、-(C=S)-C_{3-6}环烷基和-SO_2-C_{1-6}烷基；其中所述-C_{1-6}烷基的每个任选地和独立地被1至3个选自-卤素、-OH、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-C_{3-6}环烷基、-Het_2、-Ar_3和-$NR_{15}R_{16}$的取代基取代；

[0041] R_4独立地选自-卤素、-OH、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-$NR_{17}R_{18}$、-C_{3-6}环烷基、-Ar_8和-Het_4；

[0042] R_5和R_7的每个独立地选自-H、-OH、-卤素、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-Het_9、-Ar_1、-C_{3-6}环烷基、-SO_2-Ar_1、-SO_2、-SO_2-C_{1-6}烷基、-(C=O)、-(C=O)-C_{1-6}烷基、-(C=S)、-(C=S)-C_{1-6}烷基、-O-(C=O)-C_{1-6}烷基、-O-(C=S)-C_{1-6}烷基、-(C=O)-O-C_{1-6}烷基和-(C=S)-O-C_{1-6}烷基；其中所述-C_{1-6}烷基的每个任选地和独立地被1至3个选自-卤素、-OH、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-C_{3-6}环烷基、-Ar_1、-Het_9和-$NR_{23}R_{24}$的取代基取代；

[0043] R_6选自-C_{1-6}烷基、-SO_2、-SO_2-C_{1-6}烷基、-SO_2-C_{3-6}环烷基、-(C=O)、-(C=O)-C_{1-6}烷基、-(C=O)-C_{2-6}烯基、-(C=O)-O-C_{1-6}烷基、-(C=O)-Het_6、-(C=O)-Ar_6、-(C=O)-C_{3-6}环烷基、-(C=O)-$NR_{31}R_{32}$、-(C=O)-NR_{31}-(C=O)-R_{32}、-(C=S)、-(C=S)-C_{1-6}烷基、-(C=S)-C_{2-6}烯基、-(C=S)-O-C_{1-6}烷基、-(C=S)-Het_6、-(C=S)-Ar_6、-(C=S)-C_{3-6}环烷基、-(C=S)-$NR_{31}R_{32}$、-(C=S)-NR_{31}-(C=S)-R_{32}、-Het_6、-Ar_6和-C_{3-6}环烷基；

[0044] 其中所述-C_{1-6}烷基的每个任选地和独立地被1至3个选自=O、-卤素、-OH、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-C_{3-6}环烷基、-Het_6、-Ar_6、-$NR_{25}R_{26}$、-(C=O)-$NR_{25}R_{26}$、-NR_{33}(C=O)-$NR_{25}R_{26}$、-(C=S)-$NR_{25}R_{26}$和-NR_{33}(C=S)-$NR_{25}R_{26}$的取代基取代；且

[0045] 其中所述-C_{3-6}环烷基的每个任选地和独立地被1至3个选自-C_{1-6}烷基、=O、-卤素、-OH、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-Het_{12}、-Ar_{11}和-$NR_{53}R_{54}$、-(C=O)-$NR_{53}R_{54}$、-NR_{55}(C=O)-$NR_{53}R_{54}$、-(C=S)-$NR_{53}R_{54}$和-NR_{55}(C=S)-$NR_{53}R_{54}$的取代基取代；

[0046] R_8选自-NR_{34}-(C=O)-R_{35}、-NR_{34}-(C=S)-R_{35}、-NR_{36}-(C=O)-$NR_{34}R_{35}$、-NR_{36}-(C=S)-$NR_{34}R_{35}$、-NR_{34}-(SO_2)-R_{35}、-NR_{34}-(C=O)-O-R_{35}、-NR_{34}-(C=S)-O-R_{35}、-O-(C=O)-$NR_{34}R_{35}$和-O-(C=S)-$NR_{34}R_{35}$；

[0047] R_9、R_{10}、R_{11}、R_{12}、R_{13}、R_{14}、R_{15}、R_{16}、R_{17}、R_{18}、R_{19}、R_{20}、R_{21}、R_{22}、R_{23}、R_{24}、R_{25}、R_{26}、R_{27}、R_{28}、R_{29}、R_{30}、R_{31}、R_{32}、R_{33}、R_{34}、R_{35}、R_{36}、R_{37}、R_{38}、R_{39}、R_{40}、R_{44}、R_{45}、R_{46}、R_{47}、R_{48}、R_{49}、R_{50}、R_{53}、R_{54}和 R_{55}的每个独立地选自 -H、- 卤素、= O、-OH、$-C_{1-6}$烷基、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基、$-C_{3-6}$环烷基、$-Ar_5$和 $-Het_7$;其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基、$-C_{3-6}$环烷基、$-Het_7$、$-Ar_5$和 $-NR_{51}R_{52}$的取代基取代;

[0048] R_{51}和 R_{52}的每个独立地选自 -H、- 卤素、-OH、$-C_{1-6}$烷基、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基、$-C_{3-6}$环烷基、$-Ar_{10}$和 $-Het_{10}$;

[0049] R_{42}选自 -H、-OH、- 卤素、$-C_{1-6}$烷基、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基、$-NR_{46}R_{47}$、$-C_{3-6}$环烷基、$-Ar_9$和 $-Het_8$;

[0050] R_{43}选自 -H、$-C_{1-6}$烷基和 $-C_{3-6}$环烷基;其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基、$-Het_5$、$-C_{3-6}$环烷基 $-Ar_4$和 $-NR_{44}R_{45}$的取代基取代;

[0051] A 选自 $-(CH_2)_n-Y-(CH_2)_m-$、-(C = O)-、-(C = S)-、-(C = N)$-R_{49}$-、$-(SO_2)-$、$-SO_2-NR_5-$、-(C = O)$-NR_5-$、-(C = S)$-NR_5-$、$-NR_5-$(C = O)$-NR_7-$、$-NR_5-$(C = S)$-NR_7-$、$-NR_6-$、$-NR_5-$(C = O)-O-、$-NR_5-$(C = S)-O- 和 $-CHR_8-$;

[0052] X_1选自 $-C_{1-6}$烷基 -、$-O-C_{1-6}$烷基 -、$-S-C_{1-6}$烷基 -、-(C = O)-、$-NR_3-$(C = O)-、$-C_{1-6}$烷基 $-NR_3-$、$-NR_3-$、-(C = O)-、$-NR_3-$(C = O)$-NR_{48}-$、$-NR_3-C_{1-6}$烷基 -、$-NR_3-SO_2-$、$-NR_3-$(C = O)$-C_{1-6}$烷基 -、-(C = O)$-NR_3-C_{1-6}$烷基 -、$-O-C_{1-6}$烷基 $-O-C_{1-6}$烷基 - 和 $-C_{1-6}$烷基 $-NR_3-C_{1-6}$烷基 -;其中所述 $-C_{1-6}$烷基 - 的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-C_{1-6}$烷基、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基、- 苯基和 $-NR_{37}R_{38}$的取代基取代;

[0053] X_2选自 $-C_{1-6}$烷基 -、$-O-C_{1-6}$烷基 -、$-S-C_{1-6}$烷基 -、-(C = O)-、$-NR_2-$(C = O)-、$-C_{1-6}$烷基 $-NR_2-$、$-NR_2-$、-(C = O)-、$-NR_2-$(C = O)$-NR_{50}-$、$-NR_2-C_{1-6}$烷基 -、$-NR_2-SO_2-$、$-NR_2-$(C = O)$-C_{1-6}$烷基 -、-(C = O)$-NR_2-C_{1-6}$烷基 -、$-O-C_{1-6}$烷基 $-O-C_{1-6}$烷基 - 和 $-C_{1-6}$烷基 $-NR_2-C_{1-6}$烷基 -;其中所述 $-C_{1-6}$烷基 - 的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-C_{1-6}$烷基、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基、- 苯基和 $-NR_{39}R_{40}$的取代基取代;

[0054] Y 选自直接键、$-CHR_{42}-$、-O-、-S- 和 $-NR_{43}-$;

[0055] Ar_1、Ar_2、Ar_3、Ar_4、Ar_5、Ar_6、Ar_7、Ar_8、Ar_9、Ar_{10}和 Ar_{11}的每个独立地是 5- 至 10- 元的芳族杂环,其任选地包含 1 或 2 个选自 O、N 和 S 的杂原子;所述 Ar_1、Ar_2、Ar_3、Ar_4、Ar_5、Ar_6、Ar_7、Ar_8、Ar_9和 Ar_{10}的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-C_{1-6}$烷基、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基和 $-NR_{19}R_{20}$的取代基取代;其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 1 至 3 个 - 卤素取代;

[0056] Het_1、Het_2、Het_3、Het_4、Het_5、Het_6、Het_7、Het_8、Het_9、Het_{10}和 Het_{12}的每个独立地是 4- 至 10- 元的杂环,其具有 1 至 3 个选自 O、N 和 S 的杂原子,其中所述 Het_1、Het_2、Het_3、Het_4、Het_5、Het_6、Het_7、Het_8、Het_9、Het_{10}和 Het_{12}的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-C_{1-6}$烷基、$-OC_{1-6}$烷基、$-SC_{1-6}$烷基、= O、-(C = O)$-C_{1-6}$烷基和 $-NR_{21}R_{22}$的取代基取代;其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 1 至 3 个 - 卤素取代;

[0057] Z_1、Z_2、Z_3、Z_4和 Z_5的每个独立地选自 C 和 N;且

[0058] m 和 n 的每个独立地是 1、2、3 或 4。

[0059] 在另一实施方案中,本发明提供了式 I 的化合物或其立体异构体、互变异构体、外

消旋体、代谢物、前药、盐、水合物、N- 氧化物形式或溶剂化物，用于诊断、预防和 / 或治疗 RIP2- 激酶相关疾病，其中

[0060] A_1是 N，且 A_2是 C

[0061] R_1和 R_{41}的每个独立地选自 -H、- 卤素、-OH、$-C_{1\ 6}$烷基、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-NR_9R_{10}$、$-(C=O)-R_4$、$-(C=S)-R_4$、$-SO_2-R_4$、-CN、$-NR_9-SO_2-R_4$、$-C_{3\ 6}$环烷基、$-Ar_7$和 $-Het_1$；其中所述 $-C_{1\ 6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-NR_{11}R_{12}$、$-O-C_{1\ 6}$烷基和 $-S-C_{1\ 6}$烷基的取代基取代；

[0062] R_2选自 -H、- 卤素、-OH、$-C_{1\ 6}$烷基、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-(C=O)-C_{1\ 6}$烷基、$-(C=S)-C_{1\ 6}$烷基、$-(C=O)-O-C_{1\ 6}$烷基、$-(C=S)-O-C_{1\ 6}$烷基、$-(C=O)-NR_{27}R_{28}$、$-(C=S)-NR_{27}R_{28}$、$-C_{3\ 6}$环烷基、$-Het_3$、$-Ar_2$、$-(C=O)-Het_3$、$-(C=S)-Het_3$、$-(C=O)-Ar_2$、$-(C=S)-Ar_2$、$-(C=O)-C_{3\ 6}$环烷基、$-(C=S)-C_{3\ 6}$环烷基和 $-SO_2-C_{1\ 6}$烷基；其中所述 $-C_{1\ 6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-Het_3$、$-Ar_2$和 $-NR_{13}R_{14}$的取代基取代；

[0063] R_3选自 -H、- 卤素、-OH、$-C_{1\ 6}$烷基、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-(C=O)-C_{1\ 6}$烷基、$-(C=S)-C_{1\ 6}$烷基、$-(C=O)-O-C_{1\ 6}$烷基、$-(C=S)-O-C_{1\ 6}$烷基、$-(C=O)-NR_{29}R_{30}$、$-(C=S)-NR_{29}R_{30}$、$-C_{3\ 6}$环烷基、$-Het_2$、$-Ar_3$、$-(C=O)-Het_2$、$-(C=S)-Het_2$、$-(C=O)-Ar_3$、$-(C=S)-Ar_3$、$-(C=O)-C_{3\ 6}$环烷基、$-(C=S)-C_{3\ 6}$环烷基和 $-SO_2-C_{1\ 6}$烷基；其中所述 $-C_{1\ 6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-C_{3\ 6}$环烷基、$-Het_2$、$-Ar_3$和 $-NR_{15}R_{16}$的取代基取代；

[0064] R_4独立地选自 - 卤素、-OH、$-C_{1\ 6}$烷基、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-NR_{17}R_{18}$、$-C_{3\ 6}$环烷基、$-Ar_8$和 $-Het_4$；

[0065] R_5和 R_7的每个独立地选自 -H、-OH、- 卤素、$-C_{1\ 6}$烷基、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-Het_9$、$-Ar_1$、$-C_{3\ 6}$环烷基、$-SO_2-Ar_1$、$-SO_2$、$-SO_2-C_{1\ 6}$烷基、$-(C=O)$、$-(C=O)-C_{1\ 6}$烷基、$-(C=S)$、$-(C=S)-C_{1\ 6}$烷基、$-O-(C=O)-C_{1\ 6}$烷基、$-O-(C=S)-C_{1\ 6}$烷基、$-(C=O)-O-C_{1\ 6}$烷基和 $-(C=S)-O-C_{1\ 6}$烷基；其中所述 $-C_{1\ 6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-C_{3\ 6}$环烷基、$-Ar_1$、$-Het_9$和 $-NR_{23}R_{24}$的取代基取代；

[0066] R_6选自 $-C_{1\ 6}$烷基、$-SO_2$、$-SO_2-C_{1\ 6}$烷基、$-SO_2-C_{3\ 6}$环烷基、$-(C=O)$、$-(C=O)-C_{1\ 6}$烷基、$-(C=O)-C_{2\ 6}$烯基、$-(C=O)-O-C_{1\ 6}$烷基、$-(C=O)-Het_6$、$-(C=O)-Ar_6$、$-(C=O)-C_{3\ 6}$环烷基、$-(C=O)-NR_{31}R_{32}$、$-(C=O)-NR_{31}-(C=O)-R_{32}$、$-(C=S)$、$-(C=S)-C_{1\ 6}$烷基、$-(C=S)-C_{2\ 6}$烯基、$-(C=S)-O-C_{1\ 6}$烷基、$-(C=S)-Het_6$、$-(C=S)-Ar_6$、$-(C=S)-C_{3\ 6}$环烷基、$-(C=S)-NR_{31}R_{32}$、$-(C=S)-NR_{31}-(C=S)-R_{32}$、$-Het_6$、$-Ar_6$和 $-C_{3\ 6}$环烷基；

[0067] 其中所述 $-C_{1\ 6}$烷基的每个任选地和独立地被 1 至 3 个选自 =O、- 卤素、-OH、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-C_{3\ 6}$环烷基、$-Het_6$、$-Ar_6$、$-NR_{25}R_{26}$、$-(C=O)-NR_{25}R_{26}$、$-NR_{33}(C=O)-NR_{25}R_{26}$、$-(C=S)-NR_{25}R_{26}$和 $-NR_{33}(C=S)-NR_{25}R_{26}$的取代基取代；且

[0068] 其中所述 $-C_{3\ 6}$环烷基的每个任选地和独立地被 1 至 3 个选自 $-C_{1\ 6}$烷基、=O、- 卤素、-OH、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-Het_{12}$、$-Ar_{11}$和 $-NR_{53}R_{54}$、$-(C=O)-NR_{53}R_{54}$、$-NR_{55}(C=O)-NR_{53}R_{54}$、$-(C=S)-NR_{53}R_{54}$和 $-NR_{55}(C=S)-NR_{53}R_{54}$的取代基取代；

[0069] R_8选自 $-NR_{34}-(C=O)-R_{35}$、$-NR_{34}-(C=S)-R_{35}$、$-NR_{36}-(C=O)-NR_{34}R_{35}$、$-NR_{36}-(C=$

S)-$NR_{34}R_{35}$、-NR_{34}-(SO_2)-R_{35}、-NR_{34}-(C = O)-O-R_{35}、-NR_{34}-(C = S)-O-R_{35}、-O-(C = O)-$NR_{34}R_{35}$和-O-(C = S)-$NR_{34}R_{35}$;

[0070] R_9、R_{10}、R_{11}、R_{12}、R_{13}、R_{14}、R_{15}、R_{16}、R_{17}、R_{18}、R_{19}、R_{20}、R_{21}、R_{22}、R_{23}、R_{24}、R_{25}、R_{26}、R_{27}、R_{28}、R_{29}、R_{30}、R_{31}、R_{32}、R_{33}、R_{34}、R_{35}、R_{36}、R_{37}、R_{38}、R_{39}、R_{40}、R_{44}、R_{45}、R_{46}、R_{47}、R_{48}、R_{49}、R_{50}、R_{53}、R_{54}和R_{55}的每个独立地选自-H、-卤素、=O、-OH、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-C_{3-6}环烷基、-Ar_5和-Het_7;其中所述-C_{1-6}烷基的每个任选地和独立地被1至3个选自-卤素、-OH、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-C_{3-6}环烷基、-Het_7、-Ar_5和-$NR_{51}R_{52}$的取代基取代;

[0071] R_{51}和R_{52}的每个独立地选自-H、-卤素、-OH、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-C_{3-6}环烷基、-Ar_{10}和-Het_{10};

[0072] R_{42}选自-H、-OH、-卤素、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-$NR_{46}R_{47}$、-C_{3-6}环烷基、-Ar_9和-Het_8;

[0073] R_{43}选自-H、-C_{1-6}烷基和-C_{3-6}环烷基;其中所述-C_{1-6}烷基的每个任选地和独立地被1至3个选自-卤素、-OH、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-Het_5、-C_{3-6}环烷基-Ar_4和-$NR_{44}R_{45}$的取代基取代;

[0074] A选自-$(CH_2)_n$-Y-$(CH_2)_m$-、-(C = O)-、-(C = S)-、-(C = N)-R_{49}-、-(SO_2)-、-SO_2-NR_5-、-(C = O)-NR_5-、-(C = S)-NR_5-、-NR_5-(C = O)-NR_7-、-NR_5-(C = S)-NR_7-、-NR_6-、-NR_5-(C = O)-O-、-NR_5-(C = S)-O-和-CHR_8-;

[0075] X_1选自-C_{1-6}烷基-、-O-C_{1-6}烷基-、-S-C_{1-6}烷基-、-(C = O)-、-NR_3-(C = O)-、-C_{1-6}烷基-NR_3-、-NR_3-、-(C = O)-、-NR_3-(C = O)-NR_{48}-、-NR_3-C_{1-6}烷基-、-NR_3-SO_2-、-NR_3-(C = O)-C_{1-6}烷基-、-(C = O)-NR_3-C_{1-6}烷基-、-O-C_{1-6}烷基-O-C_{1-6}烷基-和-C_{1-6}烷基-NR_3-C_{1-6}烷基-;其中所述-C_{1-6}烷基-的每个任选地和独立地被1至3个选自-卤素、-OH、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-苯基和-$NR_{37}R_{38}$的取代基取代;

[0076] X_2选自-C_{1-6}烷基-、-O-C_{1-6}烷基-、-S-C_{1-6}烷基-、-(C = O)-、-NR_2-(C = O)-、-C_{1-6}烷基-NR_2-、-NR_2-、-(C = O)-、-NR_2-(C = O)-NR_{50}-、-NR_2-C_{1-6}烷基-、-NR_2-SO_2-、-NR_2-(C = O)-C_{1-6}烷基-、-(C = O)-NR_2-C_{1-6}烷基-、-O-C_{1-6}烷基-O-C_{1-6}烷基-和-C_{1-6}烷基-NR_2-C_{1-6}烷基-;其中所述-C_{1-6}烷基-的每个任选地和独立地被1至3个选自-卤素、-OH、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-苯基和-$NR_{39}R_{40}$的取代基取代;

[0077] Y选自直接键、-CHR_{42}-、-O-、-S-和-NR_{43}-;

[0078] Ar_1、Ar_2、Ar_3、Ar_4、Ar_5、Ar_6、Ar_7、Ar_8、Ar_9、Ar_{10}和Ar_{11}的每个独立地是5-至10-元的芳族杂环,其任选地包含1或2个选自O、N和S的杂原子;所述Ar_1、Ar_2、Ar_3、Ar_4、Ar_5、Ar_6、Ar_7、Ar_8、Ar_9和Ar_{10}的每个任选地和独立地被1至3个选自-卤素、-OH、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基和-$NR_{19}R_{20}$的取代基取代;其中所述-C_{1-6}烷基的每个任选地和独立地被1至3个-卤素取代;

[0079] Het_1、Het_2、Het_3、Het_4、Het_5、Het_6、Het_7、Het_8、Het_9、Het_{10}和Het_{12}的每个独立地是4-至10-元的杂环,其具有1至3个选自O、N和S的杂原子,其中所述Het_1、Het_2、Het_3、Het_4、Het_5、Het_6、Het_7、Het_8、Het_9、Het_{10}和Het_{12}的每个任选地和独立地被1至3个选自-卤素、-OH、-C_{1-6}烷基、-OC_{1-6}烷基、-SC_{1-6}烷基、=O、-(C = O)-C_{1-6}烷基和-$NR_{21}R_{22}$的取代基取代;其中所述-C_{1-6}烷基的每个任选地和独立地被1至3个-卤素取代;

[0080] Z_1、Z_2、Z_3、Z_4和Z_5的每个独立地选自C和N;且

[0081] m和n的每个独立地是1、2、3或4。

[0082] 在另一实施方案中，本发明提供了式I的化合物或其立体异构体、互变异构体、外消旋体、代谢物、前药、盐、水合物、N-氧化物形式或溶剂化物，用于诊断、预防和/或治疗RIP2-激酶相关疾病，其中

[0083] A_1和A_2选自C和N；其中当A_1是C时，则A_2是N；且其中当A_2是C时，则A_1是N；

[0084] R_1和R_{41}的每个独立地选自-H、-卤素、$-C_{1-6}$烷基、$-(C=O)-R_4$和-CN；其中所述$-C_{1-6}$烷基的每个任选地和独立地被1至3个选自$-O-C_{1-6}$烷基的取代基取代；

[0085] R_2选自-H和$-C_{1-6}$烷基；其中所述$-C_{1-6}$烷基的每个任选地和独立地被$-NR_{13}R_{14}$取代；

[0086] R_3选自-H和$-C_{1-6}$烷基；其中所述$-C_{1-6}$烷基的每个任选地和独立地被$-NR_{15}R_{16}$取代；

[0087] R_4是$-NR_{17}R_{18}$；

[0088] R_5是-H；

[0089] R_6选自$-C_{1-6}$烷基、$-(C=O)-C_{1-6}$烷基、$-(C=O)-C_{3-6}$环烷基、$-Het_6$和$-C_{3-6}$环烷基；

[0090] 其中所述$-C_{1-6}$烷基的每个任选地和独立地被1至3个选自$-O-C_{1-6}$烷基和$-Het_6$的取代基取代；

[0091] 且其中所述$-C_{3-6}$环烷基的每个任选地和独立地被1至3个选自$-C_{1-6}$烷基的取代基取代；

[0092] R_{13}、R_{14}、R_{15}、R_{16}、R_{17}、R_{18}的每个独立地选自-H和$-C_{1-6}$烷基；

[0093] R_{43}选自-H和$-C_{1-6}$烷基；

[0094] A选自$-(CH_2)_n-Y-(CH_2)_m-$、$-NR_6-$和$-(C=O)-NR_5-$；

[0095] X_1选自$-O-C_{1-6}$烷基-、$-C_{1-6}$烷基$-NR_3-$和$-C_{1-6}$烷基$-NR_3-C_{1-6}$烷基-；其中所述$-C_{1-6}$烷基-的每个任选地和独立地被1至3个选自$-C_{1-6}$烷基的取代基取代；

[0096] X_2选自$-O-C_{1-6}$烷基-、$-C_{1-6}$烷基$-NR_2-$；其中所述$-C_{1-6}$烷基-的每个任选地和独立地被1至3个选自$-C_{1-6}$烷基的取代基取代；

[0097] Y是$-NR_{43}-$；

[0098] Het_6是4-至10-元的具有1至3个选自O、N和S的杂原子的杂环；

[0099] Z_1、Z_2、Z_3、Z_4和Z_5的每个独立地选自C和N；且

[0100] m和n的每个独立地是1、2、3或4。

[0101] 在另一实施方案中，本发明提供了式I的化合物或其立体异构体、互变异构体、外消旋体、代谢物、前药、盐、水合物、N-氧化物形式或溶剂化物，用于诊断、预防和/或治疗RIP2-激酶相关疾病，其中

[0102] A_1是C，且A_2是N；

[0103] R_1和R_{41}的每个独立地选自-H、-卤素、$-C_{1-6}$烷基、$-(C=O)-R_4$和-CN；其中所述$-C_{1-6}$烷基的每个任选地和独立地被1至3个选自$-O-C_{1-6}$烷基的取代基取代；

[0104] R_2选自-H和$-C_{1-6}$烷基；其中所述$-C_{1-6}$烷基的每个任选地和独立地被$-NR_{13}R_{14}$取代；

[0105] R_3选自-H和$-C_{1-6}$烷基；其中所述$-C_{1-6}$烷基的每个任选地和独立地被$-NR_{15}R_{16}$取

代；

[0106] R_4是 $-NR_{17}R_{18}$；

[0107] R_5是 -H；

[0108] R_6选自 $-C_{1-6}$烷基、$-(C=O)-C_{1-6}$烷基、$-(C=O)-C_{3-6}$环烷基、$-Het_6$和 $-C_{3-6}$环烷基；

[0109] 其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 1 至 3 个选自 $-O-C_{1-6}$烷基和 $-Het_6$的取代基取代；

[0110] 且其中所述 $-C_{3-6}$环烷基的每个任选地和独立地被 1 至 3 个选自 $-C_{1-6}$烷基的取代基取代；

[0111] R_{13}、R_{14}、R_{15}、R_{16}、R_{17}、R_{18}的每个独立地选自 -H 和 $-C_{1-6}$烷基；

[0112] R_{43}选自 -H 和 $-C_{1-6}$烷基；

[0113] A 选自 $-(CH_2)_n-Y-(CH_2)_m-$、$-NR_6-$ 和 $-(C=O)-NR_5-$；

[0114] X_1选自 $-O-C_{1-6}$烷基 -、$-C_{1-6}$烷基 $-NR_3-$ 和 $-C_{1-6}$烷基 $-NR_3-C_{1-6}$烷基 -；其中所述 $-C_{1-6}$烷基 - 的每个任选地和独立地被 1 至 3 个选自 $-C_{1-6}$烷基的取代基取代；

[0115] X_2选自 $-O-C_{1-6}$烷基 -、$-C_{1-6}$烷基 $-NR'_2-$；其中所述 $-C_{1-6}$烷基 - 的每个任选地和独立地被 1 至 3 个选自 $-C_{1-6}$烷基的取代基取代；

[0116] Y 是 $-NR_{43}-$；

[0117] Het_6是 4- 至 10- 元的具有 1 至 3 个选自 O、N 和 S 的杂原子的杂环；

[0118] Z_1、Z_2、Z_3、Z_4和 Z_5的每个独立地选自 C 和 N；且

[0119] m 和 n 的每个独立地是 1、2、3 或 4。

[0120] 在另一实施方案中，本发明提供了式 I 的化合物或其立体异构体、互变异构体、外消旋体、代谢物、前药、盐、水合物、N- 氧化物形式或溶剂化物，用于诊断、预防和 / 或治疗 RIP2- 激酶相关疾病，其中

[0121] A_1是 N，且 A_2是 C；

[0122] R_1和 R_{41}的每个独立地选自 -H、- 卤素、$-C_{1-6}$烷基、$-(C=O)-R_4$和 -CN；其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 1 至 3 个选自 $-O-C_{1-6}$烷基的取代基取代；

[0123] R_2选自 -H 和 $-C_{1-6}$烷基；其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 $-NR_{13}R_{14}$取代；

[0124] R_3选自 -H 和 $-C_{1-6}$烷基；其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 $-NR_{15}R_{16}$取代；

[0125] R_4是 $-NR_{17}R_{18}$；

[0126] R_5是 -H；

[0127] R_6选自 $-C_{1-6}$烷基、$-(C=O)-C_{1-6}$烷基、$-(C=O)-C_{3-6}$环烷基、$-Het_6$和 $-C_{3-6}$环烷基；

[0128] 其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 1 至 3 个选自 $-O-C_{1-6}$烷基和 $-Het_6$的取代基取代；

[0129] 且其中所述 $-C_{3-6}$环烷基的每个任选地和独立地被 1 至 3 个选自 $-C_{1-6}$烷基的取代基取代；

[0130] R_{13}、R_{14}、R_{15}、R_{16}、R_{17}、R_{18}的每个独立地选自 -H 和 $-C_{1-6}$烷基；

[0131] R_{43}选自 -H 和 $-C_{1-6}$烷基；

[0132] A 选自 $-(CH_2)_n-Y-(CH_2)_m-$ 和 $-NR_6-$、$-(C=O)-NR_5-$；

[0133] X_1选自 $-O-C_{1-6}$烷基 -、$-C_{1-6}$烷基 $-NR_3-$ 和 $-C_{1-6}$烷基 $-NR_3-C_{1-6}$烷基 -；其中所述 $-C_{1-6}$烷基 - 的每个任选地和独立地被 1 至 3 个选自 $-C_{1-6}$烷基的取代基取代；

[0134] X_2选自 $-O-C_{1-6}$烷基 -、$-C_{1-6}$烷基 $-NR_2-$；其中所述 $-C_{1-6}$烷基 - 的每个任选地和独立地被 1 至 3 个选自 $-C_{1-6}$烷基的取代基取代；

[0135] Y 是 $-NR_{43}-$；

[0136] Het_6是 4- 至 10- 元的具有 1 至 3 个选自 O、N 和 S 的杂原子的杂环；

[0137] Z_1、Z_2、Z_3、Z_4和 Z_5的每个独立地选自 C 和 N；且

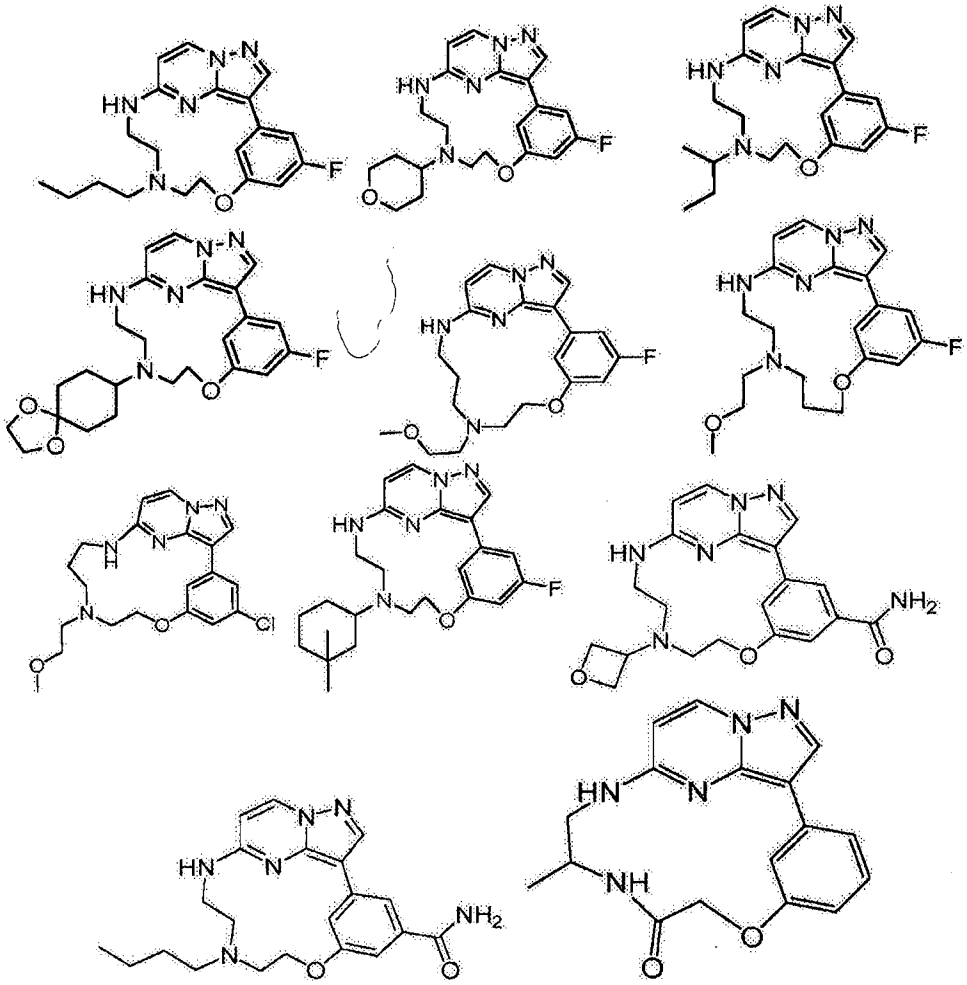
[0138] m 和 n 的每个独立地是 1、2、3 或 4。

[0139] 在另外的方面，本发明提供了用于诊断、预防和 / 或治疗 RIP2- 激酶相关疾病的本发明的化合物；其中吡唑并嘧啶或咪唑并哒嗪部分在 Z_4或 Z_5位置连接至芳基或杂芳基部分，所述位置根据式 I 中提供的编号。

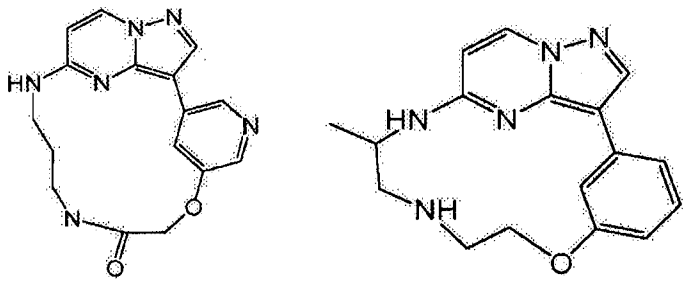
[0140] 在又一方面，本发明提供了用于诊断、预防和 / 或治疗 RIP2- 激酶相关疾病的本发明的化合物；其中 R_1在 Z_1、Z_2或 Z_3位置连接至芳基或杂芳基部分，所述位置根据式 I 中提供的编号。

[0141] 在又一方面，本发明提供了选自以下列表的化合物：

[0142]



[0143]



[0144] 在特定的实施方案中，RIP2-激酶相关疾病是炎性障碍、更特别是克罗恩病、肠疾病、结节病、银屑病、类风湿性关节炎、哮喘、溃疡性结肠炎、狼疮、眼色素层炎、blau综合征、肉芽肿性炎症、特别是贝赫切特病、多发性硬化和胰岛素抵抗性2型糖尿病。

[0145] 本发明还提供了用于预防和/或治疗RIP2-激酶相关疾病的药物组合物，其包含本发明的化合物。

[0146] 此外，本发明提供了本发明的化合物或组合物适合用于抑制激酶、特别是RIP2激酶的活性的用途；或用于诊断、预防和/或治疗RIP2-激酶相关疾病的用途。

[0147] 最后，本发明提供了预防和/或治疗RIP2-激酶相关疾病的方法；所述方法包括向有需要的受试者施用本发明的化合物或组合物。

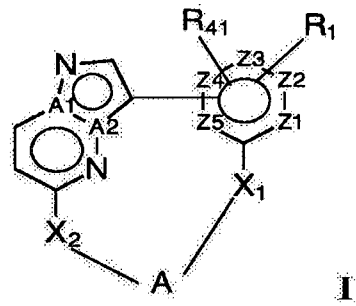
[0148] 发明详述

[0149] 现在将进一步描述本发明。在以下的段落中，更详细地定义了本发明的不同的方面。除非明确指出矛盾，所定义的每个方面可与一个或多个任意其它方面组合。具体而言，任何被表明为优选或有利的特征也可与被表明为优选或有利的一种或多种任何其它特征组合。

[0150] 除非上下文另有规定，本文中使用的星号指示单价或二价基团连接到其相关的结构以及该基团形成其一部分的结构的那个点。

[0151] 如上文已经提及的，在第一方面中，本发明提供了式I的化合物或其立体异构体、互变异构体、外消旋体、代谢物、前药、盐、水合物、N-氧化物形式或溶剂化物，用于诊断、预防和/或治疗RIP2-激酶相关疾病，

[0152]



I

[0153] 其中

[0154] A_1和A_2选自C和N；其中当A_1是C时，则A_2是N；且其中当A_2是C时，则A_1是N；

[0155] R_1和R_{41}的每个独立地选自-H、-卤素、-OH、$-C_{1-6}$烷基、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基、$-NR_9R_{10}$、$-(C=O)-R_4$、$-(C=S)-R_4$、$-SO_2-R_4$、-CN、$-NR_9-SO_2-R_4$、$-C_{3-6}$环烷基、$-Ar_7$和$-Het_1$；其中所述$-C_{1-6}$烷基的每个任选地和独立地被1至3个选自-卤素、-OH、$-NR_{11}R_{12}$、$-O-C_{1-6}$烷基和$-S-C_{1-6}$烷基的取代基取代；

[0156] R_2选自-H、-卤素、-OH、$-C_{1-6}$烷基、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基、$-(C=O)-C_{1-6}$烷基、$-(C=S)-C_{1-6}$烷基、$-(C=O)-O-C_{1-6}$烷基、$-(C=S)-O-C_{1-6}$烷基、$-(C=O)-NR_{27}R_{28}$、$-(C=S)-NR_{27}R_{28}$、$-C_{3-6}$环烷基、$-Het_3$、$-Ar_2$、$-(C=O)-Het_3$、$-(C=S)-Het_3$、$-(C=O)-Ar_2$、$-(C=S)-Ar_2$、$-(C=O)-C_{3-6}$环烷基、$-(C=S)-C_{3-6}$环烷基和$-SO_2-C_{1-6}$烷基；其中所述$-C_{1-6}$烷基的每个任选地和独立地被1至3个选自-卤素、-OH、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基、$-Het_3$、$-Ar_2$和$-NR_{13}R_{14}$的取代基取代；

[0157] R_3选自-H、-卤素、-OH、$-C_{1-6}$烷基、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基、$-(C=O)-C_{1-6}$烷基、$-(C=S)-C_{1-6}$烷基、$-(C=O)-O-C_{1-6}$烷基、$-(C=S)-O-C_{1-6}$烷基、$-(C=O)-NR_{29}R_{30}$、$-(C=S)-NR_{29}R_{30}$、$-C_{3-6}$环烷基、$-Het_2$、$-Ar_3$、$-(C=O)-Het_2$、$-(C=S)-Het_2$、$-(C=O)-Ar_3$、$-(C=S)-Ar_3$、$-(C=O)-C_{3-6}$环烷基、$-(C=S)-C_{3-6}$环烷基和$-SO_2-C_{1-6}$烷基；其中所述$-C_{1-6}$烷基的每个任选地和独立地被1至3个选自-卤素、-OH、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基、$-C_{3-6}$环烷基、$-Het_2$、$-Ar_3$和$-NR_{15}R_{16}$的取代基取代；

[0158] R_4独立地选自-卤素、-OH、$-C_{1-6}$烷基、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基、$-NR_{17}R_{18}$、$-C_{3-6}$环

烷基、-Ar_8和 -Het_4；

[0159] R_5和 R_7的每个独立地选自 -H、-OH、- 卤素、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-Het_9、-Ar_1、-C_{3-6}环烷基、-SO_2-Ar_1、-SO_2、-SO_2-C_{1-6}烷基、-(C = O)、-(C = O)-C_{1-6}烷基、-(C = S)、-(C = S)-C_{1-6}烷基、-O-(C = O)-C_{1-6}烷基、-O-(C = S)-C_{1-6}烷基、-(C = O)-O-C_{1-6}烷基和 -(C = S)-O-C_{1-6}烷基；其中所述 -C_{1-6}烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-C_{3-6}环烷基、-Ar_1、-Het_9和 -$NR_{23}R_{24}$的取代基取代；

[0160] R_6选自 -C_{1-6}烷基、-SO_2、-SO_2-C_{1-6}烷基、-SO_2-C_{3-6}环烷基、-(C = O)、-(C = O)-C_{1-6}烷基、-(C = O)-C_{2-6}烯基、-(C = O)-O-C_{1-6}烷基、-(C = O)-Het_6、-(C = O)-Ar_6、-(C = O)-C_{3-6}环烷基、-(C = O)-$NR_{31}R_{32}$、-(C = O)-NR_{31}-(C = O)-R_{32}、-(C = S)、-(C = S)-C_{1-6}烷基、-(C = S)-C_{2-6}烯基、-(C = S)-O-C_{1-6}烷基、-(C = S)-Het_6、-(C = S)-Ar_6、-(C = S)-C_{3-6}环烷基、-(C = S)-$NR_{31}R_{32}$、-(C = S)-NR_{31}-(C = S)-R_{32}、-Het_6、-Ar_6和 -C_{3-6}环烷基；

[0161] 其中所述 -C_{1-6}烷基的每个任选地和独立地被 1 至 3 个选自 = O、- 卤素、-OH、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-C_{3-6}环烷基、-Het_6、-Ar_6、-$NR_{25}R_{26}$、-(C = O)-$NR_{25}R_{26}$、-NR_{33}(C = O)-$NR_{25}R_{26}$、-(C = S)-$NR_{25}R_{26}$和 -NR_{33}(C = S)-$NR_{25}R_{26}$的取代基取代；且

[0162] 其中所述 -C_{3-6}环烷基的每个任选地和独立地被 1 至 3 个选自 -C_{1-6}烷基、= O、- 卤素、-OH、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-Het_{12}、-Ar_{11}和 -$NR_{53}R_{54}$、-(C = O)-$NR_{53}R_{54}$、-NR_{55}(C = O)-$NR_{53}R_{54}$、-(C = S)-$NR_{53}R_{54}$和 -NR_{55}(C = S)-$NR_{53}R_{54}$的取代基取代；

[0163] R_8选自 -NR_{34}-(C = O)-R_{35}、-NR_{34}-(C = S)-R_{35}、-NR_{36}-(C = O)-$NR_{34}R_{35}$、-NR_{36}-(C = S)-$NR_{34}R_{35}$、-NR_{34}-(SO_2)-R_{35}、-NR_{34}-(C = O)-O-R_{35}、-NR_{34}-(C = S)-O-R_{35}、-O-(C = O)-$NR_{34}R_{35}$和 -O-(C = S)-$NR_{34}R_{35}$；

[0164] R_9、R_{10}、R_{11}、R_{12}、R_{13}、R_{14}、R_{15}、R_{16}、R_{17}、R_{18}、R_{19}、R_{20}、R_{21}、R_{22}、R_{23}、R_{24}、R_{25}、R_{26}、R_{27}、R_{28}、R_{29}、R_{30}、R_{31}、R_{32}、R_{33}、R_{34}、R_{35}、R_{36}、R_{37}、R_{38}、R_{39}、R_{40}、R_{44}、R_{45}、R_{46}、R_{47}、R_{48}、R_{49}、R_{50}、R_{53}、R_{54}和 R_{55}的每个独立地选自 -H、- 卤素、= O、-OH、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-C_{3-6}环烷基、-Ar_5和 -Het_7；其中所述 -C_{1-6}烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-C_{3-6}环烷基、-Het_7、-Ar_5和 -$NR_{51}R_{52}$的取代基取代；

[0165] R_{51}和 R_{52}的每个独立地选自 -H、- 卤素、-OH、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-C_{3-6}环烷基、-Ar_{10}和 -Het_{10}；

[0166] R_{42}选自 -H、-OH、- 卤素、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-$NR_{46}R_{47}$、-C_{3-6}环烷基、-Ar_9和 -Het_8；

[0167] R_{43}选自 -H、-C_{1-6}烷基和 -C_{3-6}环烷基；其中所述 -C_{1-6}烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-Het_5、-C_{3-6}环烷基 -Ar_4和 -$NR_{44}R_{45}$的取代基取代；

[0168] A 选自 -(CH_2)$_n$-Y-(CH_2)$_m$-、-(C = O)-、-(C = S)-、-(C = N)-R_{49}-、-(SO_2)-、-SO_2-NR_5-、-(C = O)-NR_5-、-(C = S)-NR_5-、-NR_5-(C = O)-NR_7-、-NR_5-(C = S)-NR_7-、-NR_6-、-NR_5-(C = O)-O-、-NR_5-(C = S)-O- 和 -CHR_8-；

[0169] X_1选自 -C_{1-6}烷基 -、-O-C_{1-6}烷基 -、-S-C_{1-6}烷基 -、-(C = O)-、-NR_3-(C = O)-、-C_{1-6}烷基 -NR_3-、-NR_3-、-(C = O)-、-NR_3-(C = O)-NR_{48}-、-NR_3-C_{1-6}烷基 -、-NR_3-SO_2-、-NR_3-(C = O)-C_{1-6}烷基 -、-(C = O)-NR_3-C_{1-6}烷基 -、-O-C_{1-6}烷基 -O-C_{1-6}烷基 - 和 -C_{1-6}烷基 -NR_3-C_{1-6}

烷基－；其中所述 $-C_{1\ 6}$烷基－的每个任选地和独立地被 1 至 3 个选自－卤素、-OH、$-C_{1\ 6}$烷基、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、－苯基和 $-NR_{37}R_{38}$的取代基取代；

[0170] X_2选自 $-C_{1\ 6}$烷基－、$-O-C_{1\ 6}$烷基－、$-S-C_{1\ 6}$烷基－、$-(C=O)-$、$-NR_2-(C=O)-$、$-C_{1\ 6}$烷基 $-NR_2-$、$-NR_2-$、$-(C=O)-$、$-NR_2-(C=O)-NR_{50}-$、$-NR_2-C_{1\ 6}$烷基－、$-NR_2-SO_2-$、$-NR_2-(C=O)-C_{1\ 6}$烷基－、$-(C=O)-NR_2-C_{1\ 6}$烷基－、$-O-C_{1\ 6}$烷基 $-O-C_{1\ 6}$烷基－和 $-C_{1\ 6}$烷基 $-NR_2-C_{1\ 6}$烷基－；其中所述 $-C_{1\ 6}$烷基－的每个任选地和独立地被 1 至 3 个选自－卤素、-OH、$-C_{1\ 6}$烷基、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、－苯基和 $-NR_{39}R_{40}$的取代基取代；

[0171] Y 选自直接键、$-CHR_{42}-$、-O-、-S- 和 $-NR_{43}-$；

[0172] Ar_1、Ar_2、Ar_3、Ar_4、Ar_5、Ar_6、Ar_7、Ar_8、Ar_9、Ar_{10}和 Ar_{11}的每个独立地是 5- 至 10- 元的芳族杂环，其任选地包含 1 或 2 个选自 O、N 和 S 的杂原子；所述 Ar_1、Ar_2、Ar_3、Ar_4、Ar_5、Ar_6、Ar_7、Ar_8、Ar_9和 Ar_{10}的每个任选地和独立地被 1 至 3 个选自－卤素、-OH、$-C_{1\ 6}$烷基、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基和 $-NR_{19}R_{20}$的取代基取代；其中所述 $-C_{1\ 6}$烷基的每个任选地和独立地被 1 至 3 个－卤素取代；

[0173] Het_1、Het_2、Het_3、Het_4、Het_5、Het_6、Het_7、Het_8、Het_9、Het_{10}和 Het_{12}的每个独立地是 4- 至 10- 元的杂环，其具有 1 至 3 个选自 O、N 和 S 的杂原子，其中所述 Het_1、Het_2、Het_3、Het_4、Het_5、Het_6、Het_7、Het_8、Het_9、Het_{10}和 Het_{12}的每个任选地和独立地被 1 至 3 个选自－卤素、-OH、$-C_{1\ 6}$烷基、$-OC_{1\ 6}$烷基、$-SC_{1\ 6}$烷基、=O、$-(C=O)-C_{1\ 6}$烷基和 $-NR_{21}R_{22}$的取代基取代；其中所述 $-C_{1\ 6}$烷基的每个任选地和独立地被 1 至 3 个－卤素取代；

[0174] Z_1、Z_2、Z_3、Z_4和 Z_5的每个独立地选自 C 和 N；且

[0175] m 和 n 的每个独立地是 1、2、3 或 4。

[0176] 除非另外指定，所有上述基团可以从两个方向理解。例如，当 A 是 $-(C=O)-NR_5-$ 时，$-(C=O)-$ 可连接于 X_2，且 $-NR_5-$ 连接于 X_1。或者，$-(C=O)-$ 可连接于 X_1，且 $-NR_5-$ 连接于 X_1。例如当 A 是 $-(C=O)-NR_5-$ 时，被称为基团的“左半部分”的是 $-(C=O)-$，“右半部分”是 $-NR_5-$。

[0177] 优选地，A 例如是 A 的可能值的左半部分（即具体而言，$-(C=N)-R_{49}$中的 $-(C=N)$，$-(C=O)-NR_5$中的 $-(C=O)$，$-(C=S)-NR_5$中的 $-(C=S)$，$-SO_2-NR_5-$ 中的 $-SO_2$等）连接于 X_1。或者，A 例如是 A 的可能值的右半部分（即具体而言，$-(C=N)R_{49}$中的 $(R_{49})-$，$-(C=O)-NR_5$中的 $(NR_5)-$，$-(C=S)-NR_5$中的 $-NR_5$，$-SO_2-NR_5-$ 中的 $-NR_5-$ 等）连接于 X_1。

[0178] 优选地，X_1例如是 X_1的可能值的左半部分（即具体而言，$-O-C_{1\ 6}$烷基中的 -O，$-S-C_{1\ 6}$烷基中的 -S，$-NR_3-(C=O)$ 和 $-NR_3-C_{1\ 6}$烷基中的 $-NR_3$，$-SO_2-NR_3$中的 $-SO_2$等）连接于所述 Z_1-Z_5芳基或杂芳基部分。或者，X_1例如是 X_1的可能值的右半部分（即具体而言，$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基和 $-NR_3-C_{1\ 6}$烷基中的 $(C_{1\ 6}$烷基$)-$，$-NR_3-(C=O)$ 中的 $-(C=O)$，$-SO_2-NR_3$中的 $(NR_3)-$ 等）连接于所述 Z_1-Z_5芳基或杂芳基部分。

[0179] 优选地，X_2例如是 X_2的可能值的左半部分（即具体而言，$-O-C_{1\ 6}$烷基中的 -O，$-S-C_{1\ 6}$烷基中的 -S，$-(C=O)-NR_2$中的 $-(C=O)$，$-NR_2-C_{1\ 6}$烷基中的 $-NR_2$，$-SO_2-NR_2$中的 $-SO_2$等）连接于所述吡唑并嘧啶部分。或者，X_2例如是 X_2的可能值的右半部分（即具体而言，$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基和 $-NR_2-C_{1\ 6}$烷基中的 $(C_{1\ 6}$烷基$)-$，$-(C=O)-NR_2$和 $-SO_2-NR_2$中的 $(NR_2)-$ 等）连接于所述吡唑并嘧啶部分。

[0180] 除非另外说明，相同的原则适用于本发明所有基团。

[0181] 当描述本发明的化合物时，除非文中另有规定，否则所用术语将按下列定义来诠释：

[0182] 术语“烷基”自身或作为另一取代基的一部分是指完全饱和的烃基。一般来说，本发明的烷基包含1至6个碳原子。烷基可以是直链或支链，并可如本文所指出的被取代。当碳原子之后加上了下标，那该下标是指所命名基团可能包含的碳原子数量。因此，例如，$C_{1\ 6}$烷基是指具有1至6个碳原子的烷基。烷基的实例是甲基、乙基、正丙基、异丙基、丁基及其异构体（例如正丁基、异丁基及叔丁基）；戊基及其异构体、己基及其异构体。C_1-C_6烷基包括所有具有1至6个碳原子的直链、支链或环烷基，且因此包括甲基、乙基、正丙基、异丙基、丁基及其异构体（例如正丁基、异丁基及叔丁基）；戊基及其异构体、己基及其异构体、环丙基、环丁基、环戊基和环己基。

[0183] 术语“任选地被取代的烷基”是指在任何可用的连接点被一个或多个取代基（例如1至3个取代基、例如1、2或3个取代基或1至2个取代基）任选地取代的烷基。此类取代基的非限制性实例包括 - 卤素、-OH、伯酰胺和仲酰胺、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、杂芳基、芳基等。

[0184] 术语“环烷基”自身或作为另一取代基的一部分是指环状烷基，即，是具有环状结构的单价的、饱和的或不饱和的烃基。环烷基包括所有的饱和的或部分饱和的（含1或2个双键）、具有环状结构的烃基。环烷基在环中可包含3个或更多个碳原子，且通常根据本发明包含3至6个原子。环烷基的实例包括但不限于环丙基、环丁基、环戊基、环己基。

[0185] 本文提及的环烷基还包括被取代的环烷基，其中所述基团可被一次或多次取代，且优选被取代一次、两次或三次。取代基可选自-$C_{1\ 6}$烷基和上文所定义的那些取代的烷基。

[0186] 若所定义的烷基为二价的，即具有连接其他两个基团的两个单键，它们将被称为“亚烷基”基团。亚烷基的非限制实例包括亚甲基、亚乙基、甲基亚甲基、三亚甲基、亚丙基、四亚甲基、乙基亚乙基、1,2-二甲基亚乙基、五亚甲基及六亚甲基。

[0187] 通常，本发明的亚烷基优选包含与它们的烷基相应物相同数量的碳原子。如存在亚烷基或亚环烷基二基，那将会通过共同的碳原子或不同的碳原子连接至其形成一部分的分子结构。为了说明这一点，使用本发明的星号命名法，C_3亚烷基基团可能是例如*-$CH_2CH_2CH_2$-*、*-CH(-CH_2CH_3)-*或*-CH_2CH(-CH_3)-*。同样地，C3亚环烷基可能是

[0188]

[0189] 如本文使用的术语“杂环”自身或作为另一个基团的一部分是指非芳族的、完全饱和或部分不饱和的环状基团（例如，3至6元的单环环系统，或8-10元的二环），其在至少一个含碳原子环中具有至少一个杂原子。包含杂原子的杂环基团的每个环可具有1、2、3或4个选自氮原子、氧原子和/或硫原子的杂原子。任选地被取代的杂环是指任选地具有一个或多个取代基的杂环（如1至4个取代基、或如1、2、3或4个取代基），所述取代基选自上文所定义的那些取代的烷基。

[0190] 示例性的杂环基团包括哌啶基、氮杂环丁基、咪唑啉基、咪唑烷基、异噁唑啉基、噁唑烷基、异噁唑烷基、噻唑烷基、异噻唑烷基、哌啶基、琥珀酰亚氨基、3H-吲哚基、异二氢氮杂茚基、色烯基、异苯并二氢吡喃基、呫吨基、2H-吡咯基、1-吡咯啉基、2-吡咯啉

基、3- 吡咯啉基、吡咯烷基、4H- 喹嗪基、4aH- 咔唑基、2- 氧代哌嗪基、哌嗪基、高哌嗪基、2- 吡唑啉基、3- 吡唑啉基、吡喃基、二氢 -2H- 吡喃基、4H- 吡喃基、3, 4- 二氢 -2H- 吡喃基、酞嗪基、氧杂环丁基、硫杂环丁烷基、3- 二氧戊环基、1, 3- 二噁烷基、2, 5- 二氧咪唑烷基 (2, 5-dioximidazolidinyl)、2, 2, 4- 哌啶酮基、2- 氧代哌啶基、2- 氧代吡咯烷基 (2-oxopyrrolodinyl)、2- 氧代氮杂[illegible]基、二氢吲哚基、四氢吡喃基、四氢呋喃基、四氢噻吩基、四氢喹啉基、四氢异喹啉基、硫代吗啉基、硫代吗啉基亚砜、硫代吗啉基砜、1, 3- 二氧戊环基、1, 4- 氧硫杂环己烷基、1, 4- 二噻烷基 (1, 4-dithianyl)、1, 3, 5- 三氧杂环庚烷基 (1, 3, 5-trioxanyl)、6H-1, 2, 5- 噻二嗪基、2H-1, 5, 2- 二噻嗪基、2H-oxocinyl、1H-pyrrolizinyl、四氢 -1, 1- 二氧代噻吩基、N- 甲酰基哌嗪基和吗啉基 ;特别是吡咯烷基、咪唑烷基、吡唑烷基、哌啶基、二氧戊环基、二噁烷基、吗啉基、硫代吗啉基、哌嗪基、噻唑烷基、四氢吡喃基和四氢呋喃基。

[0191] 8-10 元的杂环基团还意在包括螺 - 基团，其是两个环通过单个原子连接在一起的二环化合物，例如螺 [4. 5] 癸烷，其是由环己烷环和环戊烷环组成的螺化合物。

[0192] 如本文使用的术语“芳基”是指具有 5-10 个原子的多元不饱和的、芳族的烃基。芳基还旨在包含本文列举的碳环系统的部分氢化的衍生物。芳基的非限制性实例包含苯基、联苯基、亚联苯基、5- 或 6- 四氢萘基、1-、2-、3-、4-、5-、6-、7- 或 8- 奠基、1- 或 2- 萘基、1-、2- 或 3- 茚基、1-、2- 或 9- 蒽基、1-、2-、3-、4- 或 5- 苊基 (acenaphtylenyl)、3-、4- 或 5- 二氢苊基 (acenaphtenyl)、1-、2-、3-、4- 或 10- 菲基、1- 或 2- 并环戊二烯基、1、2-、3- 或 4- 芴基、4- 或 5- 二氢化茚基、5-、6-、7- 或 8- 四氢萘基、1, 2, 3, 4- 四氢萘基、1, 4- 二氢萘基、二苯并 [a, d] 环庚烯基和 1-、2-、3-、4- 或 5- 苊基 ;特别是苯基。

[0193] 芳基环可以任选地被一个或多个取代基取代。“任选地被取代的芳基”是指在任何可用的连接点具有任选地一个或多个取代基 (例如 1 至 5 个取代基、例如 1、2、3 或 4 个取代基) 的芳基，所述取代基选自上文所定义的那些取代的烷基。

[0194] 如果芳基中的碳原子被杂原子所替代，由此产生的环在本文中被称作杂芳基环。

[0195] 如本文使用的术语“杂芳基”自身或作为另一基团的一部分，是指但不限于 5 至 10 个碳原子的芳族环，其中一个或多个碳原子可被氧、氮或硫原子所替代。此类杂芳基的非限制性实例包括 :吡咯基、呋喃基、噻吩基、吡唑基、咪唑基、噁唑基、异噁唑基、噻唑基、异噻唑基、三唑基、噁二唑基、噻二唑基、四唑基、噁三唑基、噻三唑基、吡啶基、嘧啶基、吡嗪基、哒嗪基、噁嗪基、二噁烯基、噻嗪基、三嗪基、咪唑并 [2, 1-b][1, 3] 噻唑基、噻吩并 [3, 2-b] 呋喃基、噻吩并 [3, 2-b] 噻吩基、噻吩并 [2, 3-d][1, 3] 噻唑基、噻吩并 [2, 3-d] 咪唑基、四唑并 [1, 5-a] 吡啶基、吲哚基、中氮茚基、异吲哚基、苯并呋喃基、异苯并呋喃基、苯并噻吩基、异苯并噻吩基、吲唑基、苯并咪唑基、1, 3- 苯并噁唑基、1, 2- 苯并异噁唑基、2, 1- 苯并异噁唑基、1, 3- 苯并噻唑基、1, 2- 苯并异噻唑基、2, 1- 苯并异噻唑基、苯并三唑基、1, 2, 3- 苯并噁二唑基、2, 1, 3- 苯并噁二唑基、1, 2, 3- 苯并噻二唑基、2, 1, 3- 苯并噻二唑基、噻吩并吡啶基、嘌呤基、咪唑并 [1, 2-a] 吡啶基、6- 氧代 - 哒嗪 -1(6H)- 基、2- 氧代吡啶 -1(2H)- 基、6- 氧代 - 哒嗪 -1(6H)- 基、2- 氧代吡啶 -1(2H)- 基、1, 3- 苯并间二氧杂环戊烯基、喹啉基、异喹啉基、噌啉基、喹唑啉基、喹喔啉基、7- 氮杂吲哚基、6- 氮杂吲哚基、5- 氮杂吲哚基、4- 氮杂吲哚基。

[0196] “任选地被取代的杂芳基”是指任选地具有一个或多个取代基 (例如 1 至 4 个取代

基、例如 1、2、3 或 4 个取代基）的杂芳基，所述取代基选自上文所定义的那些取代的烷基。

[0197] 作为基团或基团的一部分的术语卤素（halo 或 halogen）一般是氟、氯、溴或碘以及其任何适合的同位素。

[0198] 每当在本发明中使用术语“被取代的”时，它意在表明，在使用“被取代的”的表述中指出的原子上的一个或多个氢被选自指定组的基团所替代，条件是指定的原子的正常化合价不被超越，且该取代会产生化学稳定的化合物，即这样的化合物：其足够稳定以耐受从反应混合物分离至有用的纯度级别、以及配制成治疗剂和 / 或诊断剂。

[0199] 在基团可任选地被取代时，这类基团可能被取代一次或多次，且优选地一次、两次或三次。取代基可以选自上文所定义的那些取代的烷基。

[0200] 如本文使用的术语诸如“每个任选地被……取代的烷基、芳基或环烷基”或“任选地被……取代的烷基、芳基或环烷基”是指任选地被取代的烷基、任选地被取代的芳基和任选地被取代的环烷基。

[0201] 更一般而言，从上述所见，技术人员将清楚知道本发明的化合物可能会以不同的异构体和 / 或互变异构体的形式存在，包括但不限于几何异构体、构象异构体、E/Z- 异构体、立体化学异构体（即对映异构体和非对映异构体）及对应于本发明化合物中环的不同位置的相同取代基的异构体。所有这些可能的异构体、互变异构体及它们的混合物将被纳入发明的范围内。

[0202] 此外，本发明包括同位素标记的化合物和盐，其与式（I）化合物相同，但事实上一个或多个原子被具有与自然界中最常发现的原子质量或质量数不同的原子质量或质量数的原子所替代。可以掺入式（I）化合物的同位素的实例为氢、碳、氮、氟的同位素、诸如 ^{3}H、^{11}C、^{13}N、^{14}C、^{15}O 和 ^{18}F。此类同位素标记的式（I）化合物可用于药物和 / 或底物组织分布测定中。例如 ^{11}C 和 ^{18}F 同位素可特别用于 PET（正电子发射断层成象术）中。PET 可用作诊断或治疗跟踪工具，其可以以翻译的方式被应用于临床前和临床环境。其还应用于确定化合物的 PK，包括生物分布。同位素标记的式（I）化合物一般可以通过进行如下文公开的操作来制备：通过用同位素标记的试剂取代容易获得的非同位素标记的试剂。

[0203] 每当在本发明中使用术语“本发明的化合物”或类似术语时，意在包括通式 I 的化合物和它们的任意子集。这个术语也指表 1 所示的化合物、它们的衍生物、N- 氧化物、盐、溶剂化物、水合物、立体异构形式、外消旋混合物、互变异构形式、光学异构体、类似物、前药、酯和代谢物、以及它们的季铵化的氮类似物。所述化合物的 N- 氧化物形式旨在包含这样的化合物：其中一个或多个氮原子被氧化成所谓的 N- 氧化物。

[0204] 如在说明书和所附权利要求书中使用的，除非上下文另外清楚地指出，否则单数形式“一”（“a”、“an”）和“该”（“the”）包括复数指示物。作为例子，“化合物”是指一种或超过一种化合物。

[0205] 本领域技术人员较好地理解上文描述的术语和在说明书中使用的其它术语。

[0206] 在一个特定的实施方案中，本发明提供了式 I 的化合物或其立体异构体、互变异构体、外消旋体、代谢物、前药、盐、水合物、N- 氧化物形式或溶剂化物；其用于诊断、预防和 / 或治疗 RIP2- 激酶相关疾病；其中以下一项或多项适用：

[0207] A_1 和 A_2 选自 C 和 N；其中当 A_1 是 C 时，则 A_2 是 N；且其中当 A_2 是 C 时，则 A_1 是 N；

[0208] R_1 和 R_{41} 的每个独立地选自 -H、- 卤素、-OH、$-C_{1\text{-}6}$ 烷基、$-O-C_{1\text{-}6}$ 烷基、$-S-C_{1\text{-}6}$ 烷

基、$-NR_9R_{10}$、$-(C=O)-R_4$、$-(C=S)-R_4$、$-SO_2-R_4$、-CN、$-NR_9-SO_2-R_4$、$-C_{3\ 6}$环烷基、$-Ar_{7}$和 $-Het_{1}$；其中所述 $-C_{1\ 6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-NR_{11}R_{12}$、$-O-C_{1\ 6}$烷基和 $-S-C_{1\ 6}$烷基的取代基取代；

[0209] R_2选自 -H、- 卤素、-OH、$-C_{1\ 6}$烷基、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-(C=O)-C_{1\ 6}$烷基、$-(C=S)-C_{1\ 6}$烷基、$-(C=O)-O-C_{1\ 6}$烷基、$-(C=S)-O-C_{1\ 6}$烷基、$-(C=O)-NR_{27}R_{28}$、$-(C=S)-NR_{27}R_{28}$、$-C_{3\ 6}$环烷基、$-Het_{3}$、$-Ar_2$、$-(C=O)-Het_3$、$-(C=S)-Het_3$、$-(C=O)-Ar_2$、$-(C=S)-Ar_2$、$-(C=O)-C_{3\ 6}$环烷基、$-(C=S)-C_{3\ 6}$环烷基和 $-SO_2-C_{1\ 6}$烷基；其中所述 $-C_{1\ 6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-Het_{3}$、$-Ar_2$和 $-NR_{13}R_{14}$的取代基取代；

[0210] R_3选自 -H、- 卤素、-OH、$-C_{1\ 6}$烷基、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-(C=O)-C_{1\ 6}$烷基、$-(C=S)-C_{1\ 6}$烷基、$-(C=O)-O-C_{1\ 6}$烷基、$-(C=S)-O-C_{1\ 6}$烷基、$-(C=O)-NR_{29}R_{30}$、$-(C=S)-NR_{29}R_{30}$、$-C_{3\ 6}$环烷基、$-Het_{2}$、$-Ar_3$、$-(C=O)-Het_2$、$-(C=S)-Het_2$、$-(C=O)-Ar_3$、$-(C=S)-Ar_3$、$-(C=O)-C_{3\ 6}$环烷基、$-(C=S)-C_{3\ 6}$环烷基和 $-SO_2-C_{1\ 6}$烷基；其中所述 $-C_{1\ 6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-C_{3\ 6}$环烷基、$-Het_2$、$-Ar_3$和 $-NR_{15}R_{16}$的取代基取代；

[0211] R_4独立地选自 - 卤素、-OH、$-C_{1\ 6}$烷基、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-NR_{17}R_{18}$、$-C_{3\ 6}$环烷基、$-Ar_8$和 $-Het_{4}$；

[0212] R_5和 R_7的每个独立地选自 -H、-OH、- 卤素、$-C_{1\ 6}$烷基、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-Het_9$、$-Ar_1$、$-C_{3\ 6}$环烷基、$-SO_2-Ar_1$、$-SO_2$、$-SO_2-C_{1\ 6}$烷基、$-(C=O)$、$-(C=O)-C_{1\ 6}$烷基、$-(C=S)$、$-(C=S)-C_{1\ 6}$烷基、$-O-(C=O)-C_{1\ 6}$烷基、$-O-(C=S)-C_{1\ 6}$烷基、$-(C=O)-O-C_{1\ 6}$烷基和 $-(C=S)-O-C_{1\ 6}$烷基；其中所述 $-C_{1\ 6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-C_{3\ 6}$环烷基、$-Ar_{1}$、$-Het_9$和 $-NR_{23}R_{24}$的取代基取代；

[0213] R_6选自 $-C_{1\ 6}$烷基、$-SO_2$、$-SO_2-C_{1\ 6}$烷基、$-SO_2-C_{3\ 6}$环烷基、$-(C=O)$、$-(C=O)-C_{1\ 6}$烷基、$-(C=O)-C_{2\ 6}$烯基、$-(C=O)-O-C_{1\ 6}$烷基、$-(C=O)-Het_6$、$-(C=O)-Ar_6$、$-(C=O)-C_{3\ 6}$环烷基、$-(C=O)-NR_{31}R_{32}$、$-(C=O)-NR_{31}-(C=O)-R_{32}$、$-(C=S)$、$-(C=S)-C_{1\ 6}$烷基、$-(C=S)-C_{2\ 6}$烯基、$-(C=S)-O-C_{1\ 6}$烷基、$-(C=S)-Het_6$、$-(C=S)-Ar_6$、$-(C=S)-C_{3\ 6}$环烷基、$-(C=S)-NR_{31}R_{32}$、$-(C=S)-NR_{31}-(C=S)-R_{32}$、$-Het_6$、$-Ar_6$和 $-C_{3\ 6}$环烷基；

[0214] 其中所述 $-C_{1\ 6}$烷基的每个任选地和独立地被1至3个选自=O、- 卤素、-OH、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-C_{3\ 6}$环烷基、$-Het_6$、$-Ar_6$、$-NR_{25}R_{26}$、$-(C=O)-NR_{25}R_{26}$、$-NR_{33}(C=O)-NR_{25}R_{26}$、$-(C=S)-NR_{25}R_{26}$和 $-NR_{33}(C=S)-NR_{25}R_{26}$的取代基取代；且

[0215] 其中所述 $-C_{3\ 6}$环烷基的每个任选地和独立地被 1 至 3 个选自 $-C_{1\ 6}$烷基、=O、- 卤素、-OH、$-O-C_{1\ 6}$烷基、$-S-C_{1\ 6}$烷基、$-Het_{12}$、$-Ar_{11}$和 $-NR_{53}R_{54}$、$-(C=O)-NR_{53}R_{54}$、$-NR_{55}(C=O)-NR_{53}R_{54}$、$-(C=S)-NR_{53}R_{54}$和 $-NR_{55}(C=S)-NR_{53}R_{54}$的取代基取代；

[0216] R_8选自 $-NR_{34}-(C=O)-R_{35}$、$-NR_{34}-(C=S)-R_{35}$、$-NR_{36}-(C=O)-NR_{34}R_{35}$、$-NR_{36}-(C=S)-NR_{34}R_{35}$、$-NR_{34}-(SO_2)-R_{35}$、$-NR_{34}-(C=O)-O-R_{35}$、$-NR_{34}-(C=S)-O-R_{35}$、$-O-(C=O)-NR_{34}R_{35}$和 $-O-(C=S)-NR_{34}R_{35}$；

[0217] R_9、R_{10}、R_{11}、R_{12}、R_{13}、R_{14}、R_{15}、R_{16}、R_{17}、R_{18}、R_{19}、R_{20}、R_{21}、R_{22}、R_{23}、R_{24}、R_{25}、R_{26}、R_{27}、R_{28}、R_{29}、R_{30}、R_{31}、R_{32}、R_{33}、R_{34}、R_{35}、R_{36}、R_{37}、R_{38}、R_{39}、R_{40}、R_{44}、R_{45}、R_{46}、R_{47}、R_{48}、R_{49}、R_{50}、R_{53}、R_{54}和 R_{55}的每个

独立地选自 -H、- 卤素、= O、-OH、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-C_{3-6}环烷基、-Ar_5和 -Het_7;其中所述 -C_{1-6}烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-C_{3-6}环烷基、-Het_7、-Ar_5和 -$NR_{51}R_{52}$的取代基取代；

[0218] R_{51}和 R_{52}的每个独立地选自 -H、- 卤素、-OH、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-C_{3-6}环烷基、-Ar_{10}和 -Het_{10}；

[0219] R_{42}选自 -H、-OH、- 卤素、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-$NR_{46}R_{47}$、-C_{3-6}环烷基、-Ar_9和 -Het_8；

[0220] R_{43}选自 -H、-C_{1-6}烷基和 -C_{3-6}环烷基；其中所述 -C_{1-6}烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-Het_5、-C_{3-6}环烷基 -Ar_4和 -$NR_{44}R_{45}$的取代基取代；

[0221] A 选自 $-(CH_2)_n-Y-(CH_2)_m-$、-(C = O)-、-(C = S)-、-(C = N)-R_{49}-、-(SO_2)-、-SO_2-NR_5-、-(C = O)-NR_5-、-(C = S)-NR_5-、-NR_5-(C = O)-NR_7-、-NR_5-(C = S)-NR_7-、-NR_6-、-NR_5-(C = O)-O-、-NR_5-(C = S)-O- 和 -CHR_8-；

[0222] X_1选自 -C_{1-6}烷基 -、-O-C_{1-6}烷基 -、-S-C_{1-6}烷基 -、-(C = O)-、-NR_3-(C = O)-、-C_{1-6}烷基 -NR_3-、-NR_3-、-(C = O)-、-NR_3-(C = O)-NR_{18}-、-NR_3-C_{1-6}烷基 -、-NR_3-SO_2-、-NR_3-(C = O)-C_{1-6}烷基 -、-(C = O)-NR_3-C_{1-6}烷基 -、-O-C_{1-6}烷基 -O-C_{1-6}烷基 - 和 -C_{1-6}烷基 -NR_3-C_{1-6}烷基 -；其中所述 -C_{1-6}烷基 - 的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基、- 苯基和 -$NR_{37}R_{38}$的取代基取代；

[0223] X_2选自 -C_{1-6}烷基 -、-O-C_{1-6}烷基 -、-S-C_{1-6}烷基 -、-(C = O)-、-NR_2-(C = O)-、-C_{1-6}烷基 -NR_2-、-NR_2-、-(C = O)-、-NR_2-(C = O)-NR_{50}-、-NR_2-C_{1-6}烷基 -、-NR_2-SO_2-、-NR_2-(C = O)-C_{1-6}烷基 -、-(C = O)-NR_2-C_{1-6}烷基 -、-O-C_{1-6}烷基 -O-C_{1-6}烷基 - 和 -C_{1-6}烷基 -NR_2-C_{1-6}烷基 -；其中所述 -C_{1-6}烷基 - 的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基、- 苯基和 -$NR_{39}R_{40}$的取代基取代；

[0224] Y 选自直接键、-CHR_{42}-、-O-、-S- 和 -NR_{43}-；

[0225] Ar_1、Ar_2、Ar_3、Ar_4、Ar_5、Ar_6、Ar_7、Ar_8、Ar_9、Ar_{10}和 Ar_{11}的每个独立地是 5- 至 10- 元的芳族杂环，其任选地包含 1 或 2 个选自 O、N 和 S 的杂原子；所述 Ar_1、Ar_2、Ar_3、Ar_4、Ar_5、Ar_6、Ar_7、Ar_8、Ar_9和 Ar_{10}的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基和 -$NR_{19}R_{20}$的取代基取代；其中所述 -C_{1-6}烷基的每个任选地和独立地被 1 至 3 个 - 卤素取代；

[0226] Het_1、Het_2、Het_3、Het_4、Het_5、Het_6、Het_7、Het_8、Het_9、Het_{10}和 Het_{12}的每个独立地是 4- 至 10- 元的杂环，其具有 1 至 3 个选自 O、N 和 S 的杂原子，其中所述 Het_1、Het_2、Het_3、Het_4、Het_5、Het_6、Het_7、Het_8、Het_9、Het_{10}和 Het_{12}的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、-C_{1-6}烷基、-OC_{1-6}烷基、-SC_{1-6}烷基、= O、-(C = O)-C_{1-6}烷基和 -$NR_{21}R_{22}$的取代基取代；其中所述 -C_{1-6}烷基的每个任选地和独立地被 1 至 3 个 - 卤素取代；

[0227] Z_1、Z_2、Z_3、Z_4和 Z_5的每个独立地选自 C 和 N；且

[0228] m 和 n 的每个独立地是 1、2、3 或 4；

[0229] 特别地，如本文使用的 X_1和 X_2表示二基，其与它们所连接的基团一起形成大环吡唑并嘧啶化合物。所述二基可以在大环吡唑并嘧啶中以两个方向中的任何一个存在，但是优选以下文所述的方向存在：

[0230] 对于式 I：

[0231] X_1选自 *-$C_{1\ 6}$烷基 -、*-O-$C_{1\ 6}$烷基 -、*-S-$C_{1\ 6}$烷基 -、*-(C = O)-、-NR_3-(C = O)-、*-$C_{1\ 6}$烷基 -NR_3-、*-NR_3-、*-(C = O)-、*-NR_3-(C = O)-NR_{48}-、*-NR_3-$C_{1\ 6}$烷基 -、*-NR_3-SO_2-、*-NR_3-(C = O)-$C_{1\ 6}$烷基 -、*-(C = O)-NR_3-$C_{1\ 6}$烷基 -、*-O-$C_{1\ 6}$烷基 -O-$C_{1\ 6}$烷基 - 和 *-$C_{1\ 6}$烷基 -NR_3-$C_{1\ 6}$烷基 -；其中所述二基优选通过 * 连接于芳基或杂芳基部分；

[0232] X_2选自 *-$C_{1\ 6}$烷基 -、*-O-$C_{1\ 6}$烷基 -、*-S-$C_{1\ 6}$烷基 -、*-(C = O)-、*-NR_2-(C = O)-、*-$C_{1\ 6}$烷基 -NR_2-、*-NR_2-、*-(C = O)-、*-NR_2-(C = O)-NR_{50}-、*-NR_2-$C_{1\ 6}$烷基 -、*-NR_2-SO_2-、*-NR_2-(C = O)-$C_{1\ 6}$烷基 -、*-(C = O)-NR_2-$C_{1\ 6}$烷基 -、*-O-$C_{1\ 6}$烷基 -O-$C_{1\ 6}$烷基 - 和 *-$C_{1\ 6}$烷基 -NR_2-$C_{1\ 6}$烷基 -；其中所述二基优选通过 * 连接于吡唑并嘧啶部分；

[0233] 在一个优选的实施方案中，本发明提供了式 I 的化合物或其立体异构体、互变异构体、外消旋体、代谢物、前药、盐、水合物、N- 氧化物形式或溶剂化物，用于诊断、预防和 / 或治疗 RIP2- 激酶相关疾病，其中

[0234] A_1是 C，且 A_2是 N；

[0235] R_1和 R_{41}的每个独立地选自 -H、- 卤素、-OH、-$C_{1\ 6}$烷基、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、-NR_9R_{10}、-(C = O)-R_4、-(C = S)-R_4、-SO_2-R_4、-CN、-NR_9-SO_2-R_4、-$C_{3\ 6}$环烷基、-Ar_7和 -Het_1；其中所述 -$C_{1\ 6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、-$NR_{11}R_{12}$、-O-$C_{1\ 6}$烷基和 -S-$C_{1\ 6}$烷基的取代基取代；

[0236] R_2选自 -H、- 卤素、-OH、-$C_{1\ 6}$烷基、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、-(C = O)-$C_{1\ 6}$烷基、-(C = S)-$C_{1\ 6}$烷基、-(C = O)-O-$C_{1\ 6}$烷基、-(C = S)-O-$C_{1\ 6}$烷基、-(C = O)-$NR_{27}R_{28}$、-(C = S)-$NR_{27}R_{28}$、-$C_{3\ 6}$环烷基、-Het_3、-Ar_2、-(C = O)-Het_3、-(C = S)-Het_3、-(C = O)-Ar_2、-(C = S)-Ar_2、-(C = O)-$C_{3\ 6}$环烷基、-(C = S)-$C_{3\ 6}$环烷基和 -SO_2-$C_{1\ 6}$烷基；其中所述 -$C_{1\ 6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、-Het_3、-Ar_2和 -$NR_{13}R_{14}$的取代基取代；

[0237] R_3选自 -H、- 卤素、-OH、-$C_{1\ 6}$烷基、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、-(C = O)-$C_{1\ 6}$烷基、-(C = S)-$C_{1\ 6}$烷基、-(C = O)-O-$C_{1\ 6}$烷基、-(C = S)-O-$C_{1\ 6}$烷基、-(C = O)-$NR_{29}R_{30}$、-(C = S)-$NR_{29}R_{30}$、-$C_{3\ 6}$环烷基、-Het_2、-Ar_3、-(C = O)-Het_2、-(C = S)-Het_2、-(C = O)-Ar_3、-(C = S)-Ar_3、-(C = O)-$C_{3\ 6}$环烷基、-(C = S)-$C_{3\ 6}$环烷基和 -SO_2-$C_{1\ 6}$烷基；其中所述 -$C_{1\ 6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、-$C_{3\ 6}$环烷基、-Het_2、-Ar_3和 -$NR_{15}R_{16}$的取代基取代；

[0238] R_4独立地选自 - 卤素、-OH、-$C_{1\ 6}$烷基、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、-$NR_{17}R_{18}$、-$C_{3\ 6}$环烷基、-Ar_8和 -Het_4；

[0239] R_5和 R_7的每个独立地选自 -H、-OH、- 卤素、-$C_{1\ 6}$烷基、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、-Het_9、-Ar_1、-$C_{3\ 6}$环烷基、-SO_2-Ar_1、-SO_2、-SO_2-$C_{1\ 6}$烷基、-(C = O)、-(C = O)-$C_{1\ 6}$烷基、-(C = S)、-(C = S)-$C_{1\ 6}$烷基、-O-(C = O)-$C_{1\ 6}$烷基、-O-(C = S)-$C_{1\ 6}$烷基、-(C = O)-O-$C_{1\ 6}$烷基和 -(C = S)-O-$C_{1\ 6}$烷基；其中所述 -$C_{1\ 6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、-$C_{3\ 6}$环烷基、-Ar_1、-Het_9和 -$NR_{23}R_{24}$的取代基取代；

[0240] R_6选自 -$C_{1\ 6}$烷基、-SO_2、-SO_2-$C_{1\ 6}$烷基、-SO_2-$C_{3\ 6}$环烷基、-(C = O)、-(C = O)-$C_{1\ 6}$烷基、-(C = O)-$C_{2\ 6}$烯基、-(C = O)-O-$C_{1\ 6}$烷基、-(C = O)-Het_6、-(C = O)-Ar_6、-(C = O)-$C_{3\ 6}$

环烷基、-(C = O)-$NR_{31}R_{32}$、-(C = O)-NR_{31}-(C = O)-R_{32}、-(C = S)、-(C = S)-C_{1-6}烷基、-(C = S)-C_{2-6}烯基、-(C = S)-O-C_{1-6}烷基、-(C = S)-Het_{6}、-(C = S)-Ar_6、-(C = S)-C_{3-6}环烷基、-(C = S)-$NR_{31}R_{32}$、-(C = S)-NR_{31}-(C = S)-R_{32}、$-Het_6$、$-Ar_6$和 $-C_{3-6}$环烷基；

[0241] 其中所述-C_{1-6}烷基的每个任选地和独立地被1至3个选自=O、-卤素、-OH、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-C_{3-6}环烷基、$-Het_{6}$、$-Ar_6$、$-NR_{25}R_{26}$、-(C = O)-$NR_{25}R_{26}$、$-NR_{33}$(C = O)-$NR_{25}R_{26}$、-(C = S)-$NR_{25}R_{26}$和 $-NR_{33}$(C = S)-$NR_{25}R_{26}$的取代基取代；且

[0242] 其中所述-C_{3-6}环烷基的每个任选地和独立地被1至3个选自-C_{1-6}烷基、=O、-卤素、-OH、-O-C_{1-6}烷基、-S-C_{1-6}烷基、$-Het_{12}$、$-Ar_{11}$和 $-NR_{53}R_{54}$、-(C = O)-$NR_{53}R_{54}$、$-NR_{55}$(C = O)-$NR_{53}R_{54}$、-(C = S)-$NR_{53}R_{54}$和 $-NR_{55}$(C = S)-$NR_{53}R_{54}$的取代基取代；

[0243] R_8选自 $-NR_{34}$-(C = O)-R_{35}、$-NR_{34}$-(C = S)-R_{35}、$-NR_{36}$-(C = O)-$NR_{34}R_{35}$、$-NR_{36}$-(C = S)-$NR_{34}R_{35}$、$-NR_{34}$-(SO_2)-R_{35}、$-NR_{34}$-(C = O)-O-R_{35}、$-NR_{34}$-(C = S)-O-R_{35}、-O-(C = O)-$NR_{34}R_{35}$和 -O-(C = S)-$NR_{34}R_{35}$；

[0244] R_9、R_{10}、R_{11}、R_{12}、R_{13}、R_{14}、R_{15}、R_{16}、R_{17}、R_{18}、R_{19}、R_{20}、R_{21}、R_{22}、R_{23}、R_{24}、R_{25}、R_{26}、R_{27}、R_{28}、R_{29}、R_{30}、R_{31}、R_{32}、R_{33}、R_{34}、R_{35}、R_{36}、R_{37}、R_{38}、R_{39}、R_{40}、R_{44}、R_{45}、R_{46}、R_{47}、R_{48}、R_{49}、R_{50}、R_{53}、R_{54}和 R_{55}的每个独立地选自 -H、-卤素、=O、-OH、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-C_{3-6}环烷基、$-Ar_5$和 $-Het_7$；其中所述-C_{1-6}烷基的每个任选地和独立地被1至3个选自-卤素、-OH、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-C_{3-6}环烷基、$-Het_{7}$、$-Ar_5$和 $-NR_{51}R_{52}$的取代基取代；

[0245] R_{51}和 R_{52}的每个独立地选自 -H、-卤素、-OH、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-C_{3-6}环烷基、$-Ar_{10}$和 $-Het_{10}$；

[0246] R_{12}选自 -H、-OH、-卤素、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基、$-NR_{46}R_{47}$、-C_{3-6}环烷基、$-Ar_9$和 $-Het_8$；

[0247] R_{43}选自 -H、-C_{1-6}烷基和 -C_{3-6}环烷基；其中所述-C_{1-6}烷基的每个任选地和独立地被1至3个选自-卤素、-OH、-O-C_{1-6}烷基、-S-C_{1-6}烷基、$-Het_5$、-C_{3-6}环烷基 $-Ar_4$和 $-NR_{44}R_{45}$的取代基取代；

[0248] A选自 $-(CH_2)_n-Y-(CH_2)_m-$、-(C = O)-、-(C = S)-、-(C = N)-R_{49}-、-(SO_2)-、$-SO_2-NR_5-$、-(C = O)-NR_5-、-(C = S)-NR_5-、$-NR_5$-(C = O)-NR_7-、$-NR_5$-(C = S)-NR_7-、$-NR_6$-、$-NR_5$-(C = O)-O-、$-NR_5$-(C = S)-O-和 $-CHR_8$-；

[0249] X_1选自-C_{1-6}烷基-、-O-C_{1-6}烷基-、-S-C_{1-6}烷基-、-(C = O)-、$-NR_3$-(C = O)-、-C_{1-6}烷基-NR_3-、$-NR_3$-、-(C = O)-、$-NR_3$-(C = O)-NR_{48}-、$-NR_3-C_{1-6}$烷基-、$-NR_3-SO_2$-、$-NR_3$-(C = O)-C_{1-6}烷基-、-(C = O)-NR_3-C_{1-6}烷基-、-O-C_{1-6}烷基-O-C_{1-6}烷基-和-C_{1-6}烷基-NR_3-C_{1-6}烷基-；其中所述-C_{1-6}烷基-的每个任选地和独立地被1至3个选自-卤素、-OH、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-苯基和 $-NR_{37}R_{38}$的取代基取代；

[0250] X_2选自-C_{1-6}烷基-、-O-C_{1-6}烷基-、-S-C_{1-6}烷基-、-(C = O)-、$-NR_2$-(C = O)-、-C_{1-6}烷基-NR_2-、$-NR_2$-、-(C = O)-、$-NR_2$-(C = O)-NR_{50}-、$-NR_2-C_{1-6}$烷基-、$-NR_2-SO_2$-、$-NR_2$-(C = O)-C_{1-6}烷基-、-(C = O)-NR_2-C_{1-6}烷基-、-O-C_{1-6}烷基-O-C_{1-6}烷基-和-C_{1-6}烷基-NR_2-C_{1-6}烷基-；其中所述-C_{1-6}烷基-的每个任选地和独立地被1至3个选自-卤素、-OH、-C_{1-6}烷基、-O-C_{1-6}烷基、-S-C_{1-6}烷基、-苯基和 $-NR_{39}R_{40}$的取代基取代；

[0251] Y选自直接键、-CHR_{42}-、-O-、-S-和 $-NR_{43}$-；

[0252] Ar_1、Ar_2、Ar_3、Ar_4、Ar_5、Ar_6、Ar_7、Ar_8、Ar_9、Ar_{10}和 Ar_{11}的每个独立地是5-至10-元的

芳族杂环，其任选地包含 1 或 2 个选自 O、N 和 S 的杂原子；所述 Ar_1、Ar_2、Ar_3、Ar_4、Ar_5、Ar_6、Ar_7、Ar_8、Ar_9和 Ar_{10}的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-C_{1-6}$烷基、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基和 $-NR_{19}R_{20}$的取代基取代；其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 1 至 3 个 - 卤素取代；

[0253] Het_1、Het_2、Het_3、Het_4、Het_5、Het_6、Het_7、Het_8、Het_9、Het_{10}和 Het_{12}的每个独立地是 4- 至 10- 元的杂环，其具有 1 至 3 个选自 O、N 和 S 的杂原子，其中所述 Het_1、Het_2、Het_3、Het_4、Het_5、Het_6、Het_7、Het_8、Het_9、Het_{10}和 Het_{12}的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-C_{1-6}$烷基、$-OC_{1-6}$烷基、$-SC_{1-6}$烷基、= O、$-(C=O)-C_{1-6}$烷基和 $-NR_{21}R_{22}$的取代基取代；其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 1 至 3 个 - 卤素取代；

[0254] Z_1、Z_2、Z_3、Z_4和 Z_5的每个独立地选自 C 和 N；且

[0255] m 和 n 的每个独立地是 1、2、3 或 4。

[0256] 在另一实施方案中，本发明提供了式 I 的化合物或其立体异构体、互变异构体、外消旋体、代谢物、前药、盐、水合物、N- 氧化物形式或溶剂化物，用于诊断、预防和 / 或治疗 RIP2- 激酶相关疾病，其中

[0257] A_1是 N，且 A_2是 C

[0258] R_1和 R_{41}的每个独立地选自 -H、- 卤素、-OH、$-C_{1-6}$烷基、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基、$-NR_9R_{10}$、$-(C=O)-R_4$、$-(C=S)-R_4$、$-SO_2-R_4$、-CN、$-NR_9-SO_2-R_4$、$-C_{3-6}$环烷基、$-Ar_7$和 $-Het_1$；其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-NR_{11}R_{12}$、$-O-C_{1-6}$烷基和 $-S-C_{1-6}$烷基的取代基取代；

[0259] R_2选自 -H、- 卤素、-OH、$-C_{1-6}$烷基、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基、$-(C=O)-C_{1-6}$烷基、$-(C=S)-C_{1-6}$烷基、$-(C=O)-O-C_{1-6}$烷基、$-(C=S)-O-C_{1-6}$烷基、$-(C=O)-NR_{27}R_{28}$、$-(C=S)-NR_{27}R_{28}$、$-C_{3-6}$环烷基、$-Het_3$、$-Ar_2$、$-(C=O)-Het_3$、$-(C=S)-Het_3$、$-(C=O)-Ar_2$、$-(C=S)-Ar_2$、$-(C=O)-C_{3-6}$环烷基、$-(C=S)-C_{3-6}$环烷基和 $-SO_2-C_{1-6}$烷基；其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基、$-Het_3$、$-Ar_2$和 $-NR_{13}R_{14}$的取代基取代；

[0260] R_3选自 -H、- 卤素、-OH、$-C_{1-6}$烷基、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基、$-(C=O)-C_{1-6}$烷基、$-(C=S)-C_{1-6}$烷基、$-(C=O)-O-C_{1-6}$烷基、$-(C=S)-O-C_{1-6}$烷基、$-(C=O)-NR_{29}R_{30}$、$-(C=S)-NR_{29}R_{30}$、$-C_{3-6}$环烷基、$-Het_2$、$-Ar_3$、$-(C=O)-Het_2$、$-(C=S)-Het_2$、$-(C=O)-Ar_3$、$-(C=S)-Ar_3$、$-(C=O)-C_{3-6}$环烷基、$-(C=S)-C_{3-6}$环烷基和 $-SO_2-C_{1-6}$烷基；其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基、$-C_{3-6}$环烷基、$-Het_2$、$-Ar_3$和 $-NR_{15}R_{16}$的取代基取代；

[0261] R_4独立地选自 - 卤素、-OH、$-C_{1-6}$烷基、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基、$-NR_{17}R_{18}$、$-C_{3-6}$环烷基、$-Ar_8$和 $-Het_4$；

[0262] R_5和 R_7的每个独立地选自 -H、-OH、- 卤素、$-C_{1-6}$烷基、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基、$-Het_9$、$-Ar_1$、$-C_{3-6}$环烷基、$-SO_2-Ar_1$、$-SO_2$、$-SO_2-C_{1-6}$烷基、$-(C=O)$、$-(C=O)-C_{1-6}$烷基、$-(C=S)$、$-(C=S)-C_{1-6}$烷基、$-O-(C=O)-C_{1-6}$烷基、$-O-(C=S)-C_{1-6}$烷基、$-(C=O)-O-C_{1-6}$烷基和 $-(C=S)-O-C_{1-6}$烷基；其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-O-C_{1-6}$烷基、$-S-C_{1-6}$烷基、$-C_{3-6}$环烷基、$-Ar_1$、$-Het_9$和 $-NR_{23}R_{24}$的取代基取代；

[0263] R_6选自 $-C_{1\ 6}$烷基、$-SO_{2}$、$-SO_2-C_{1\ 6}$烷基、$-SO_{2}-C_{3\ 6}$环烷基、-(C = O)、-(C = O)$-C_{1\ 6}$烷基、-(C = O)$-C_{2\ 6}$烯基、-(C = O)-O-$C_{1\ 6}$烷基、-(C = O)$-Het_6$、-(C = O)$-Ar_6$、-(C = O)$-C_{3\ 6}$环烷基、-(C = O)$-NR_{31}R_{32}$、-(C = O)$-NR_{31}$-(C = O)$-R_{32}$、-(C = S)、-(C = S)$-C_{1\ 6}$烷基、-(C = S)$-C_{2\ 6}$烯基、-(C = S)-O-$C_{1\ 6}$烷基、-(C = S)$-Het_6$、-(C = S)$-Ar_6$、-(C = S)$-C_{3\ 6}$环烷基、-(C = S)$-NR_{31}R_{32}$、-(C = S)$-NR_{31}$-(C = S)$-R_{32}$、$-Het_6$、$-Ar_6$和 $-C_{3\ 6}$环烷基；

[0264] 其中所述$-C_{1\ 6}$烷基的每个任选地和独立地被1至3个选自=O、-卤素、-OH、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、-$C_{3\ 6}$环烷基、$-Het_6$、$-Ar_6$、$-NR_{25}R_{26}$、-(C = O)$-NR_{25}R_{26}$、$-NR_{33}$(C = O)$-NR_{25}R_{26}$、-(C = S)$-NR_{25}R_{26}$和 $-NR_{33}$(C = S)$-NR_{25}R_{26}$的取代基取代；且

[0265] 其中所述$-C_{3\ 6}$环烷基的每个任选地和独立地被1至3个选自$-C_{1\ 6}$烷基、=O、-卤素、-OH、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、$-Het_{12}$、$-Ar_{11}$和 $-NR_{53}R_{54}$、-(C = O)$-NR_{53}R_{54}$、$-NR_{55}$(C = O)$-NR_{53}R_{54}$、-(C = S)$-NR_{53}R_{54}$和 $-NR_{55}$(C = S)$-NR_{53}R_{54}$的取代基取代；

[0266] R_8选自 $-NR_{34}$-(C = O)$-R_{35}$、$-NR_{34}$-(C = S)$-R_{35}$、$-NR_{36}$-(C = O)$-NR_{34}R_{35}$、$-NR_{36}$-(C = S)$-NR_{34}R_{35}$、$-NR_{34}-(SO_2)-R_{35}$、$-NR_{34}$-(C = O)-O-R_{35}、$-NR_{34}$-(C = S)-O-R_{35}、-O-(C = O)$-NR_{34}R_{35}$和 -O-(C = S)$-NR_{34}R_{35}$；

[0267] R_9、R_{10}、R_{11}、R_{12}、R_{13}、R_{14}、R_{15}、R_{16}、R_{17}、R_{18}、R_{19}、R_{20}、R_{21}、R_{22}、R_{23}、R_{24}、R_{25}、R_{26}、R_{27}、R_{28}、R_{29}、R_{30}、R_{31}、R_{32}、R_{33}、R_{34}、R_{35}、R_{36}、R_{37}、R_{38}、R_{39}、R_{40}、R_{44}、R_{45}、R_{46}、R_{47}、R_{48}、R_{49}、R_{50}、R_{53}、R_{54}和 R_{55}的每个独立地选自 -H、-卤素、=O、-OH、$-C_{1\ 6}$烷基、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、-$C_{3\ 6}$环烷基、$-Ar_5$和 $-Het_7$；其中所述$-C_{1\ 6}$烷基的每个任选地和独立地被1至3个选自-卤素、-OH、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、-$C_{3\ 6}$环烷基、$-Het_7$、$-Ar_5$和 $-NR_{51}R_{52}$的取代基取代；

[0268] R_{51}和 R_{52}的每个独立地选自 -H、-卤素、-OH、$-C_{1\ 6}$烷基、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、-$C_{3\ 6}$环烷基、$-Ar_{10}$和 $-Het_{10}$；

[0269] R_{42}选自 -H、-OH、-卤素、$-C_{1\ 6}$烷基、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、$-NR_{46}R_{47}$、-$C_{3\ 6}$环烷基、$-Ar_9$和 $-Het_8$；

[0270] R_{43}选自 -H、$-C_{1\ 6}$烷基和 -$C_{3\ 6}$环烷基；其中所述$-C_{1\ 6}$烷基的每个任选地和独立地被1至3个选自-卤素、-OH、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、$-Het_5$、-$C_{3\ 6}$环烷基 $-Ar_4$和 $-NR_{44}R_{45}$的取代基取代；

[0271] A选自 $-(CH_2)_n-Y-(CH_2)_m-$、-(C = O)-、-(C = S)-、-(C = N)$-R_{49}$-、$-(SO_2)-$、$-SO_2-NR_5-$、-(C = O)$-NR_5-$、-(C = S)$-NR_5-$、$-NR_5$-(C = O)$-NR_7-$、$-NR_5$-(C = S)$-NR_7-$、$-NR_6-$、$-NR_5$-(C = O)-O-、$-NR_5$-(C = S)-O-和 $-CHR_8-$；

[0272] X_1选自 $-C_{1\ 6}$烷基-、-O-$C_{1\ 6}$烷基-、-S-$C_{1\ 6}$烷基-、-(C = O)-、$-NR_3$-(C = O)-、$-C_{1\ 6}$烷基$-NR_3-$、$-NR_3-$、-(C = O)-、$-NR_3$-(C = O)$-NR_{48}-$、$-NR_3-C_{1\ 6}$烷基-、$-NR_3-SO_2-$、$-NR_3$-(C = O)$-C_{1\ 6}$烷基-、-(C = O)$-NR_3-C_{1\ 6}$烷基-、-O-$C_{1\ 6}$烷基-O-$C_{1\ 6}$烷基-和 $-C_{1\ 6}$烷基$-NR_3-C_{1\ 6}$烷基-；其中所述$-C_{1\ 6}$烷基-的每个任选地和独立地被1至3个选自-卤素、-OH、$-C_{1\ 6}$烷基、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、-苯基和 $-NR_{37}R_{38}$的取代基取代；

[0273] X_2选自 $-C_{1\ 6}$烷基-、-O-$C_{1\ 6}$烷基-、-S-$C_{1\ 6}$烷基-、-(C = O)-、$-NR_2$-(C = O)-、$-C_{1\ 6}$烷基$-NR_2-$、$-NR_2-$、-(C = O)-、$-NR_2$-(C = O)$-NR_{50}-$、$-NR_2-C_{1\ 6}$烷基-、$-NR_2-SO_2-$、$-NR_2$-(C = O)$-C_{1\ 6}$烷基-、-(C = O)$-NR_2-C_{1\ 6}$烷基-、-O-$C_{1\ 6}$烷基-O-$C_{1\ 6}$烷基-和 $-C_{1\ 6}$烷基$-NR_2-C_{1\ 6}$烷基-；其中所述$-C_{1\ 6}$烷基-的每个任选地和独立地被1至3个选自-卤素、-OH、$-C_{1\ 6}$烷基、-O-$C_{1\ 6}$烷基、-S-$C_{1\ 6}$烷基、-苯基和 $-NR_{39}R_{40}$的取代基取代；

[0274] Y 选自直接键、$-CHR_{42}-$、-O-、-S- 和 $-NR_{43}-$；

[0275] Ar_1、Ar_2、Ar_3、Ar_4、Ar_5、Ar_6、Ar_7、Ar_8、Ar_9、Ar_{10}和 Ar_{11}的每个独立地是 5- 至 10- 元的芳族杂环，其任选地包含 1 或 2 个选自 O、N 和 S 的杂原子；所述 Ar_1、Ar_2、Ar_3、Ar_4、Ar_5、Ar_6、Ar_7、Ar_8、Ar_9和 Ar_{10}的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-C_{1\text{-}6}$烷基、$-O-C_{1\text{-}6}$烷基、$-S-C_{1\text{-}6}$烷基和 $-NR_{19}R_{20}$的取代基取代；其中所述 $-C_{1\text{-}6}$烷基的每个任选地和独立地被 1 至 3 个 - 卤素取代；

[0276] Het_1、Het_2、Het_3、Het_4、Het_5、Het_6、Het_7、Het_8、Het_9、Het_{10}和 Het_{12}的每个独立地是 4- 至 10- 元的杂环，其具有 1 至 3 个选自 O、N 和 S 的杂原子，其中所述 Het_1、Het_2、Het_3、Het_4、Het_5、Het_6、Het_7、Het_8、Het_9、Het_{10}和 Het_{12}的每个任选地和独立地被 1 至 3 个选自 - 卤素、-OH、$-C_{1\text{-}6}$烷基、$-OC_{1\text{-}6}$烷基、$-SC_{1\text{-}6}$烷基、=O、$-(C=O)-C_{1\text{-}6}$烷基和 $-NR_{21}R_{22}$的取代基取代；其中所述 $-C_{1\text{-}6}$烷基的每个任选地和独立地被 1 至 3 个 - 卤素取代；

[0277] Z_1、Z_2、Z_3、Z_4和 Z_5的每个独立地选自 C 和 N；且

[0278] m 和 n 的每个独立地是 1、2、3 或 4。

[0279] 在另一实施方案中，本发明提供了式 I 的化合物或其立体异构体、互变异构体、外消旋体、代谢物、前药、盐、水合物、N- 氧化物形式或溶剂化物，用于诊断、预防和 / 或治疗 RIP2- 激酶相关疾病，其中

[0280] A_1和 A_2选自 C 和 N；其中当 A_1是 C 时，则 A_2是 N；且其中当 A_2是 C 时，则 A_1是 N；

[0281] R_1和 R_{41}的每个独立地选自 -H、- 卤素、$-C_{1\text{-}6}$烷基、$-(C=O)-R_4$和 -CN；其中所述 $-C_{1\text{-}6}$烷基的每个任选地和独立地被 1 至 3 个选自 $-O-C_{1\text{-}6}$烷基的取代基取代；

[0282] R_2选自 -H 和 $-C_{1\text{-}6}$烷基；其中所述 $-C_{1\text{-}6}$烷基的每个任选地和独立地被 $-NR_{13}R_{14}$取代；

[0283] R_3选自 -H 和 $-C_{1\text{-}6}$烷基；其中所述 $-C_{1\text{-}6}$烷基的每个任选地和独立地被 $-NR_{15}R_{16}$取代；

[0284] R_4是 $-NR_{17}R_{18}$；

[0285] R_5是 -H；

[0286] R_6选自 $-C_{1\text{-}6}$烷基、$-(C=O)-C_{1\text{-}6}$烷基、$-(C=O)-C_{3\text{-}6}$环烷基、$-Het_6$和 $-C_{3\text{-}6}$环烷基；

[0287] 其中所述 $-C_{1\text{-}6}$烷基的每个任选地和独立地被 1 至 3 个选自 $-O-C_{1\text{-}6}$烷基和 $-Het_6$的取代基取代；

[0288] 且其中所述 $-C_{3\text{-}6}$环烷基的每个任选地和独立地被 1 至 3 个选自 $-C_{1\text{-}6}$烷基的取代基取代；

[0289] R_{13}、R_{14}、R_{15}、R_{16}、R_{17}、R_{18}的每个独立地选自 -H 和 $-C_{1\text{-}6}$烷基；

[0290] R_{43}选自 -H 和 $-C_{1\text{-}6}$烷基；

[0291] A 选自 $-(CH_2)_n-Y-(CH_2)_m-$ 和 $-NR_6-$、$-(C=O)-NR_5-$；

[0292] X_1选自 $-O-C_{1\text{-}6}$烷基 -、$-C_{1\text{-}6}$烷基 $-NR_3-$ 和 $-C_{1\text{-}6}$烷基 $-NR_3-C_{1\text{-}6}$烷基 -；其中所述 $-C_{1\text{-}6}$烷基 - 的每个任选地和独立地被 1 至 3 个选自 $-C_{1\text{-}6}$烷基的取代基取代；

[0293] X_2选自 $-O-C_{1\text{-}6}$烷基 -、$-C_{1\text{-}6}$烷基 $-NR_2-$；其中所述 $-C_{1\text{-}6}$烷基 - 的每个任选地和独立地被 1 至 3 个选自 $-C_{1\text{-}6}$烷基的取代基取代；

[0294] Y 是 $-NR_{43}-$；

[0295] Het_6是 4- 至 10- 元的具有 1 至 3 个选自 O、N 和 S 的杂原子的杂环；

[0296] Z_1、Z_2、Z_3、Z_4和 Z_5的每个独立地选自 C 和 N；且

[0297] m 和 n 的每个独立地是 1、2、3 或 4；

[0298] 在另一实施方案中，本发明提供了式 I 的化合物或其立体异构体、互变异构体、外消旋体、代谢物、前药、盐、水合物、N- 氧化物形式或溶剂化物，用于诊断、预防和 / 或治疗 RIP2- 激酶相关疾病，其中

[0299] A_1是 C，且 A_2是 N；

[0300] R_1和 R_{41}的每个独立地选自 -H、- 卤素、$-C_{1-6}$烷基、-(C = O)-R_4和 -CN；其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 1 至 3 个选自 -O-C_{1-6}烷基的取代基取代；

[0301] R_2选自 -H 和 $-C_{1-6}$烷基；其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 $-NR_{13}R_{14}$取代；

[0302] R_3选自 -H 和 $-C_{1-6}$烷基；其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 $-NR_{15}R_{16}$取代；

[0303] R_4是 $-NR_{17}R_{18}$；

[0304] R_5是 -H；

[0305] R_6选自 $-C_{1-6}$烷基、-(C = O)-C_{1-6}烷基、-(C = O)-C_{3-6}环烷基、$-Het_6$和 $-C_{3-6}$环烷基；

[0306] 其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 1 至 3 个选自 -O-C_{1-6}烷基和 $-Het_6$的取代基取代；

[0307] 且其中所述 $-C_{3-6}$环烷基的每个任选地和独立地被 1 至 3 个选自 $-C_{1-6}$烷基的取代基取代；

[0308] R_{13}、R_{14}、R_{15}、R_{16}、R_{17}、R_{18}的每个独立地选自 -H 和 $-C_{1-6}$烷基；

[0309] R_{43}选自 -H 和 $-C_{1-6}$烷基；

[0310] A 选自 $-(CH_2)_n-Y-(CH_2)_m-$ 和 $-NR_6-$、-(C = O)-NR_5-；

[0311] X_1选自 -O-C_{1-6}烷基 -、$-C_{1-6}$烷基 $-NR_3-$ 和 $-C_{1-6}$烷基 $-NR_3-C_{1-6}$烷基 -；其中所述 $-C_{1-6}$烷基 - 的每个任选地和独立地被 1 至 3 个选自 $-C_{1-6}$烷基的取代基取代；

[0312] X_2选自 -O-C_{1-6}烷基 -、$-C_{1-6}$烷基 $-NR_2-$；其中所述 $-C_{1-6}$烷基 - 的每个任选地和独立地被 1 至 3 个选自 $-C_{1-6}$烷基的取代基取代；

[0313] Y 是 $-NR_{43}-$；

[0314] Het_6是 4- 至 10- 元的具有 1 至 3 个选自 O、N 和 S 的杂原子的杂环；

[0315] Z_1、Z_2、Z_3、Z_4和 Z_5的每个独立地选自 C 和 N；且

[0316] m 和 n 的每个独立地是 1、2、3 或 4。

[0317] 在另一实施方案中，本发明提供了式 I 的化合物或其立体异构体、互变异构体、外消旋体、代谢物、前药、盐、水合物、N- 氧化物形式或溶剂化物，用于诊断、预防和 / 或治疗 RIP2- 激酶相关疾病，其中

[0318] A_1是 N，且 A_2是 C；

[0319] R_1和 R_{41}的每个独立地选自 -H、- 卤素、$-C_{1-6}$烷基、-(C = O)-R_4和 -CN；其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 1 至 3 个选自 -O-C_{1-6}烷基的取代基取代；

[0320] R_2选自 -H 和 $-C_{1-6}$烷基；其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 $-NR_{13}R_{14}$取

代；

[0321] R_3选自 -H 和 $-C_{1-6}$烷基；其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 $-NR_{15}R_{16}$取代；

[0322] R_4是 $-NR_{17}R_{18}$；

[0323] R_5是 -H；

[0324] R_6选自 $-C_{1-6}$烷基、$-(C=O)-C_{1-6}$烷基、$-(C=O)-C_{3-6}$环烷基、$-Het_6$和 $-C_{3-6}$环烷基；

[0325] 其中所述 $-C_{1-6}$烷基的每个任选地和独立地被 1 至 3 个选自 $-O-C_{1-6}$烷基和 $-Het_6$的取代基取代；

[0326] 且其中所述 $-C_{3-6}$环烷基的每个任选地和独立地被 1 至 3 个选自 $-C_{1-6}$烷基的取代基取代；

[0327] R_{13}、R_{14}、R_{15}、R_{16}、R_{17}、R_{18}的每个独立地选自 -H 和 $-C_{1-6}$烷基；

[0328] R_{43}选自 -H 和 $-C_{1-6}$烷基；

[0329] A 选自 $-(CH_2)_n-Y-(CH_2)_m-$、$-NR_6-$ 和 $-(C=O)-NR_5-$；

[0330] X_1选自 $-O-C_{1-6}$烷基 -、$-C_{1-6}$烷基 $-NR_3-$ 和 $-C_{1-6}$烷基 $-NR_3-C_{1-6}$烷基 -；其中所述 $-C_{1-6}$烷基 - 的每个任选地和独立地被 1 至 3 个选自 $-C_{1-6}$烷基的取代基取代；

[0331] X_2选自 $-O-C_{1-6}$烷基 -、$-C_{1-6}$烷基 $-NR_2-$；其中所述 $-C_{1-6}$烷基 - 的每个任选地和独立地被 1 至 3 个选自 $-C_{1-6}$烷基的取代基取代；

[0332] Y 是 $-NR_{43}-$；

[0333] Het_6是 4- 至 10- 元的具有 1 至 3 个选自 O、N 和 S 的杂原子的杂环；

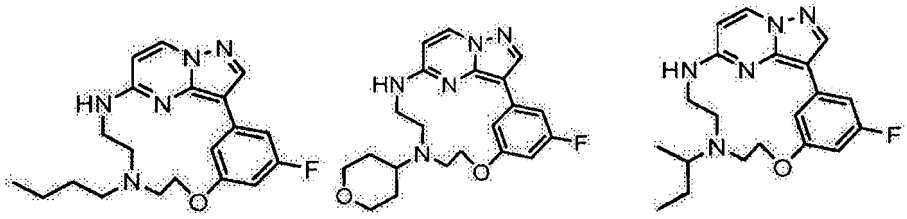
[0334] Z_1、Z_2、Z_3、Z_4和 Z_5的每个独立地选自 C 和 N；且

[0335] m 和 n 的每个独立地是 1、2、3 或 4。

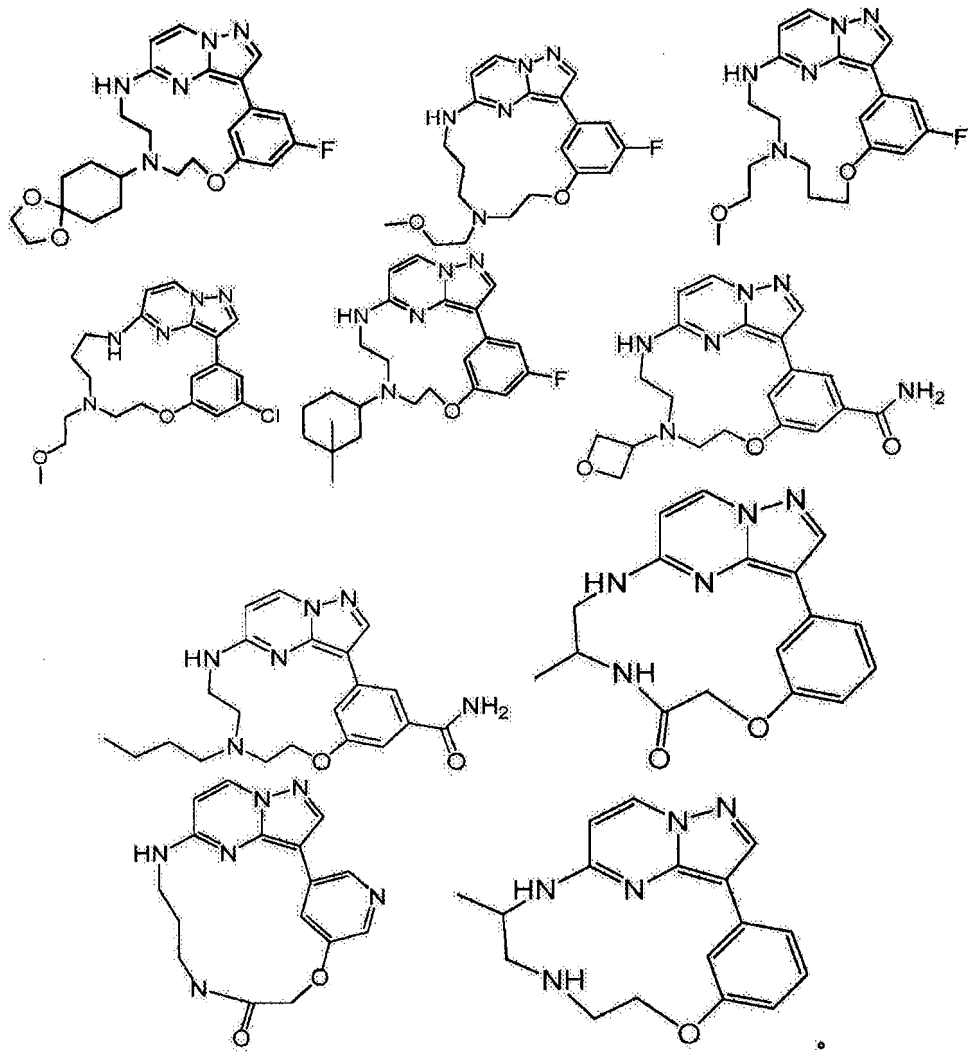
[0336] 特别地，在本发明的化合物中，吡唑并嘧啶或咪唑并哒嗪部分在 Z_4或 Z_5位连接于芳基或杂芳基部分，所述位置根据式 I 中提供的编号。此外，本发明化合物的 R_1优选在 Z_1、Z_2或 Z_3位连接于芳基或杂芳基部分，所述位置根据式 I 中提供的编号。

[0337] 在又一方面，本发明提供了选自以下的化合物：

[0338]



[0339]



[0340] 本发明的化合物可以根据以下实施例所提供的反应方案来制备，但本领域技术人员会明白这些都仅作为本发明的示范，而本发明的化合物可以根据任何有机化学技术人员的常用标准合成方法制备。

[0341] 治疗方法

[0342] 式（I）的化合物、其立体异构体、互变异构体、外消旋体、代谢物、前药、盐、水合物、N- 氧化物形式或溶剂化物是 RIP2 激酶活性抑制剂，且因此被认为在诊断、预防和 / 或治疗炎性障碍、特别是克罗恩病、肠疾病、结节病、银屑病、类风湿性关节炎、哮喘、溃疡性结肠炎、狼疮、眼色素层炎、blau 综合征、肉芽肿性炎症、特别是贝赫切特病、多发性硬化和胰岛素抵抗性 2 型糖尿病中有潜在用途。

[0343] 本文使用的术语 " 炎性障碍 " 或 " 炎性疾病 " 可以指特征为导致或引起若干急性和慢性病症的发病的免疫系统的异常活化的障碍或疾病，所述急性和慢性病症包括例如结节病、类风湿性关节炎、炎性肠病、移植排斥、结肠炎、胃炎和回肠炎。炎性疾病可以包括其中对组织损伤、细胞损伤、抗原、感染性疾病和 / 或一些未知的原因有响应的状态。炎症的

症状可包括但不限于细胞渗透和组织肿胀。

[0344] 在本发明中，特别优选的是，在下文所述对 RIP2 的抑制测定中能以小于 10 μM、优选地小于 1 μM、最优选小于 100 nM 的 IC_{50} 值抑制激酶活性的式 I 的化合物或其任何子集。

[0345] 所述的抑制可能会发生于体外和 / 或体内，当发生于体内时，优选以如上定义的选择性方式进行。

[0346] 本文中使用的术语 "RIP2 激酶介导的病症 " 或 " 疾病 " 是指已知在其中 RIP2 激酶和 / 或其突变体能发挥作用的任何疾病或其它有害的病症。术语 "RIP2 激酶介导的病症 " 或 " 疾病 " 也表示通过 RIP2 激酶抑制剂治疗缓解的疾病或病症。相应地，本发明的另一实施方案涉及治疗或减轻一种或多种 RIP2 激酶发挥作用的疾病的严重性。

[0347] 在药物用途方面，本发明的化合物可用作游离酸或碱，和 / 或以药学可接受的的酸加成盐和 / 或碱加成盐的形式（例如通过无毒性的有机或无机酸或碱获得）、以水合物、溶剂化物和 / 或络合物的形式、和 / 或以前药形式使用，诸如酯类。除另有注明外，否则本文中使用的术语 " 溶剂化物 " 包括任何用本发明化合物与适合的无机溶剂（例如水合物）或有机溶剂（例如但不限于醇类、酮类、酯类等）形成的组合。技术人员将清楚知道这类盐、水合物、溶剂化物等及其制备；例如盐、水合物、溶剂化物等的参考在 US-A-6372778、US-A-6369086、US-A-6369087 和 US-A-6372733 中记载。

[0348] 根据本发明的化合物的药学可接受的的盐，即以水可溶性、油可溶性的或可分散的产物形式呈现，包括从例如无机或有机酸或碱形成的常规无毒性盐或季铵盐。这样的酸加成盐的实例包括：乙酸盐、己二酸盐、藻酸盐、天冬氨酸盐、苯甲酸盐、苯磺酸盐、硫酸氢盐、丁酸盐、柠檬酸盐、樟脑酸盐、樟脑磺酸盐、环戊烷丙酸盐、二葡萄糖酸盐、十二烷基硫酸盐、乙磺酸盐、富马酸盐、葡萄糖庚酸盐、甘油磷酸盐、半硫酸盐、庚酸盐、己酸盐、盐酸盐、氢溴酸盐、氢碘酸盐、2- 羟基乙磺酸盐、乳酸盐、马来酸盐、甲磺酸盐、2- 萘磺酸盐、烟酸盐、草酸盐、棕榈酸盐、果胶酸盐、过硫酸盐、3- 苯基丙酸盐、苦味酸盐、新戊酸盐、丙酸盐、琥珀酸盐、酒石酸盐、硫氰酸盐、甲苯磺酸盐和十一烷酸盐。碱盐包括铵盐、碱金属盐诸如钠盐和钾盐、碱土金属盐诸如钙盐和镁盐、与有机碱形成的盐诸如二环己胺盐、N- 甲基 -D- 葡糖胺、和与诸如精氨酸、赖氨酸等氨基酸形成的盐。此外，碱性含氮基团可用诸如下述试剂季铵化：低级烷基卤化物、诸如甲基、乙基、丙基和丁基的氯化物、溴化物和碘化物；二烷基硫酸酯如二甲基、二乙基、二丁基和二戊基硫酸酯；长链卤化物诸如癸基、月桂基、肉豆蔻基和硬脂酰基的氯化物、溴化物和碘化物；芳烷基卤化物如苄基和苯乙基溴化物等。其它药学可接受的的盐包括硫酸盐乙醇化物和硫酸盐。

[0349] 通常，对于制药用途而言，本发明的化合物可以被配制为药物制剂或药物组合物，其包含至少一种本发明化合物和至少一种药学可接受的的载体、稀释剂或赋形剂和 / 或辅料、以及任选地一种或多种其它的药学活性化合物。

[0350] 通过非限制性实例，此类制剂可以是适合口服施用、胃肠外施用（诸如通过静脉内、肌内或皮下注射或静脉输注）、吸入施用、通过皮肤贴剂、通过植入物、通过栓剂等的形式。该类适合的施用形式（基于施用方式，可能是固体、半固体或液体形式）以及其制备方法和用于其制备的载体，稀释剂及赋形剂，都将为技术人员熟知；可再次参见例如 US-A-6372778、US-A-6369086、US-A-6369087 和 US-A-6372733，以及诸如最新版本 Remington's Pharmaceutical Sciences 的标准手册。

[0351] 这类制剂的某些优选但非限制性的实例包括片剂、丸剂、粉剂、锭剂、小药囊、扁囊剂、酏剂、混悬剂、乳剂、溶液剂、糖浆剂、气雾剂、软膏剂、霜剂、洗剂、软和硬明胶胶囊剂、栓剂、滴眼剂、用作推注和/或连续施用的无菌注射溶液剂和无菌包装的粉末剂(通常使用前需重新构建),所述剂型可以用本身适用于这些剂型的以下载体、赋形剂及稀释剂进行配制,例如乳糖、葡萄糖、蔗糖、山梨醇、甘露醇、淀粉、金合欢树胶、磷酸钙、藻酸盐、黄蓍胶、明胶、硅酸钙、微晶纤维素、聚乙烯吡咯烷酮、聚乙二醇、纤维素、(无菌)水、甲基纤维素、羟基苯甲酸甲酯和羟基苯甲酸丙酯、滑石粉、硬脂酸镁、食用油、植物油和矿物油或其合适的混合物。制剂可以任选地含有其它药学活性物质(可能会或不会与本发明的化合物产生协同作用)及在药物制剂中常用的其它物质,诸如润滑剂、润湿剂、乳化剂和助悬剂、分散剂、崩解剂、膨胀剂、填充剂、防腐剂、甜味剂、矫味剂、流动调节剂、释放剂等。还可以配制组合物以提供其中所含的活性化合物的快速、持续或延迟释放,例如使用脂质体或基于天然的凝胶或合成聚合物的亲水性聚合基质。为了增强本发明药物组合物的化合物的溶解度和/或稳定性,采用α、β-和γ-环糊精及其衍生物是有益的。一种与环糊精及其衍生物组合来配制化合物的令人感兴趣的方法已经在EP-A-721331中记载。特别地,本发明包括的药物组合物包含有效量的本发明化合物及药学可接受的的环糊精。

[0352] 此外,诸如醇类的共溶剂可改善化合物的溶解度和/或稳定性。在制备水性组合物时,加入本发明化合物的盐可以更适合,这是因为它们的水溶性更高。

[0353] 对于局部施用,喷雾剂、软膏剂或透皮贴剂或其它适用于局部、经皮和/或皮内施用形式的化合物可能是有益的。

[0354] 更具体而言,组合物可以制成包含治疗有效量的由本发明的化合物的固体分散体和一种或多种药学可接受的的水溶性的聚合物组成的颗粒的药物制剂。

[0355] 术语"固体分散体"的定义为包含至少有两个成分的固态(相对液态或气态)系统,其中一个成分能或多或少均匀地分散到其它一种或多种成分中。当所述成分分散性使得系统在化学和物理性质上统一或各处均质或由热力学上定义的单相组成,这类固体分散体将被称为"固体溶液"。固体溶液是一种优选的物理系统,这是因为其中成分对所施用的生物体通常是生物可利用的。

[0356] 以纳米粒子的形式配制化合物可能会进一步带来方便,所述纳米粒子具有吸附在其表面的、足以将有效平均粒径维持在小于1000nm的量的表面改性剂。合适的表面改性剂可以优选选自已知的有机及无机药物赋形剂。这类赋形剂包括各种聚合物、低分子量寡聚物、天然产物及表面活性剂。优选的表面改性剂包括非离子及阴离子表面活性剂。

[0357] 另一配制本发明化合物的令人感兴趣的方法包括药物组合物,其中将化合物掺入亲水性聚合物中,然后将这种混合物作为涂覆膜涂在许多小珠上,从而得到可方便制备且适用于制备口服用的药物剂型的具有良好生物利用度的组合物。用于在小珠中作为核心的材料可以是多样的,只要所述材料是药学可接受的的并具有适当的尺寸及硬度。这种材料的实例是聚合物、无机物质、有机物质、糖类及其衍生物。

[0358] 该制剂可用本身已知的方式制备,这通常涉及混合至少一种本发明的化合物及一种或多种药学可接受的载体,如果需要的话,当必要时在无菌条件下,与其它药物活性化合物组合。再次参考US-A-6,372,778、US-A-6,369,086、US-A-6,369,087和US-A-6,372,733以及标准手册,诸如Remington的Pharmaceutical Sciences的最新版。

[0359] 本发明的药物制剂优选制成单位剂型或适当地被包装，例如盒、泡罩、小瓶、瓶、小药囊、安瓿或任何其它合适的单剂量或多剂量的支持物或容器（贴有适当标签）；任选地具有一个或更多包含产品信息和/或使用说明的小册子。一般来说，该单位剂量将包含至少一种1和1000mg之间、且通常5和500mg之间的本发明化合物，例如每单位剂量约10、25、50、100、200、300或400mg。

[0360] 所述化合物可以通过多种途径施用，包括口服、直肠、眼、透皮、皮下、静脉内、肌内或鼻内途径，主要取决于所用的具体制剂及需治疗或预防的病症，且通常优选口服和静脉内施用。至少一种本发明化合物通常以"有效量"施用，也就是说在适当施用后足以在被施用的个体中实现期望的治疗或预防效果的式化合物或其任何子集的任意量。通常取决于要预防或治疗的病症及施用途径，该有效量通常会是每日每千克患者体重0.01至1000 mg之间，更经常是0.1至500mg之间，例如1至250mg之间，例如每日每千克患者体重约5、10、20、50、100、150、200或250 mg，能够以每日单剂量，将每日剂量分成一次或多次，或基本上持续给药，例如使用点滴注射。治疗医生可能会根据诸如患者的年龄、性别、一般状况及待治疗疾病/症状的性质及严重性的因素来决定施用量、给药途径及进一步的治疗方案。再次参考US-A-6372778,US-A-6369086、US-A-6369087和US-A-6372733，和上文提及的其它现有技术，以及诸如最新版本Remington's Pharmaceutical Sciences的标准手册。

[0361] 按照本发明的方法，所述的药物组合物可以在治疗过程中分别在不同的时间施用或同时以分开的或单一的组合形式施用。因此，本发明应被理解为涵盖所有这些同时或交替的治疗方案，而术语"施用"将会相应地被作出诠释。

[0362] 对于口服形式，本发明的组合物可以与合适的添加剂混合，例如赋形剂、稳定剂或惰性稀释剂，并使用习惯的方式转换成合适的施用形式，例如片剂、包衣片剂、硬胶囊剂、水溶液剂、醇溶液剂、或油性溶液剂。合适惰性载体的实例是阿拉伯树胶、氧化镁、碳酸镁、磷酸钾、乳糖、葡萄糖或淀粉，特别是玉米淀粉。在这种情况下，既可以配制为干燥的颗粒，也可以配制为润湿的颗粒。合适的油性赋形剂或溶剂是植物油或动物油，如葵花油或鳕鱼肝油。水溶液或醇溶液的合适溶剂是水、乙醇、糖溶液或其混合物。聚乙二醇和聚丙二醇也为适用于其它施用形式的另外的助剂。作为立即释放的片剂，这些组合物可以含有微晶纤维素、磷酸二钙、淀粉、硬脂酸镁和乳糖和/或本领域已知的其它赋形剂、粘合剂、增量剂、崩解剂、稀释剂和润滑剂。

[0363] 当通过鼻腔气雾剂或吸入施用时，这些组合物可以根据药物制剂领域众所周知的技术制备，并可以制备成盐水溶液，采用苯甲醇或其它合适的防腐剂、吸收促进剂以提高生物利用度，并采用本领域已知的氟碳化合物和/或其它增溶剂或分散剂。用于以气雾剂或喷雾剂形式施用的适合的药物制剂为例如本发明化合物的溶液剂、悬浮剂或乳剂，或其在药学可接受的溶剂（例如乙醇或水）中的生理耐受盐，或此类溶剂的混合物。如需要，所述制剂另外还可以包含其它药物助剂，例如表面活性剂、乳化剂、稳定剂及推进剂。

[0364] 对于皮下施用，如需要，可以用常规物质（诸如增溶剂、乳化剂或其它助剂）将本发明的化合物配制成溶液剂、混悬剂或乳剂。本发明的化合物也可被冻干，而所获取的冻干粉剂用于例如生产注射或输注制剂。适当的溶剂为，例如水、生理盐水溶液或醇，例如乙醇、丙醇、甘油，此外还有糖溶液、诸如葡萄糖溶液或甘露醇溶液、或者以上提到的各种溶剂的其他混合物。注射溶液剂或混悬剂可根据本领域已知的技术配制，使用合适的无毒、胃肠外

可接受的稀释剂或溶剂，诸如甘露醇、1,3-丁二醇、水、林格氏液或等渗氯化钠溶液，或者适合的分散剂或湿润剂及助悬剂，诸如无菌、无刺激性、不挥发性油，包括人工合成的单甘酯或甘油二酯，及脂肪酸，包括油酸。

[0365] 当以栓剂形式直肠施用时，这些制剂可能通过混合本发明化合物及合适的非刺激性赋形剂来制备，所述非刺激性赋形剂为例如可可脂、合成甘油酯或聚乙二醇，它们在一般温度下呈固体状态，但在直肠腔中会液化和/或溶解，以释放出药物。

[0366] 在优选的实施方案中，本发明的化合物和组合物经口服或胃肠外施用。

[0367] 现在将通过下面的合成实施例和生物的实施例来解释本发明，但是其不以任何方式限制本发明的范围。

实施例

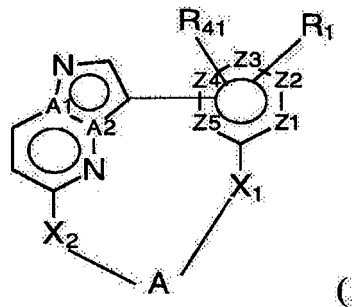
[0368] A. 化合物合成和理化性质

[0369] 本发明的化合物可以根据有机化学领域技术人员常用的若干标准合成方法中任何一种来制备。所述化合物通常从商购得到的原料或通过本领域技术人员显而易见的标准方法制备的起始物质来制备。

[0370] 通用方案：

[0371] 如上文表明，本发明提供了用于诊断、预防和/或治疗 RIP2-激酶相关疾病的式 I 的化合物：

[0372]



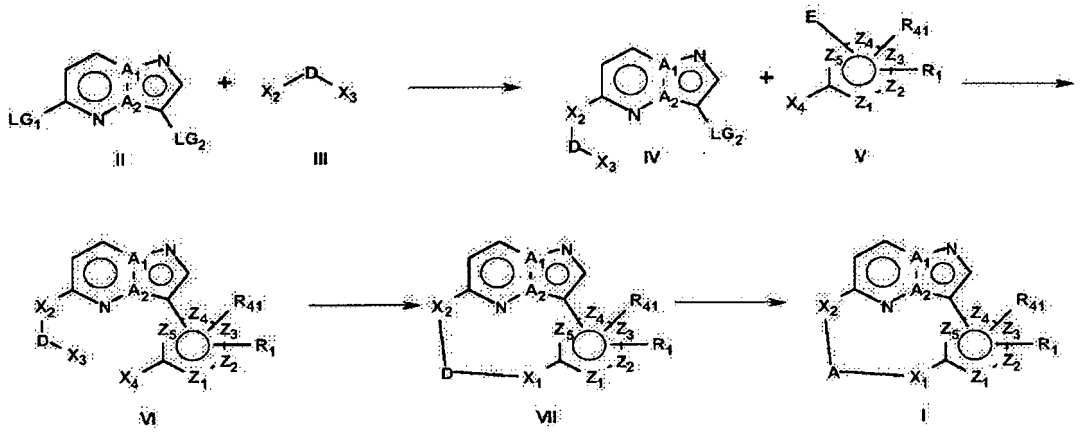
(I)

[0373] 关于适用于制备所述化合物的通用反应方案，这些化合物可以分别由式 Ia 或 Ib 表示，下文可以见用于其的通用反应方案。

[0374] 通常式 (I) 化合物可以如以下方案 1 所示来制备，其中通过与式 (III) 化合物反应将式 (II) 的吡唑并 [1,5-a] 嘧啶或咪唑并 [2,1-f] 哒嗪转化为式 (IV) 的化合物，然后将其与式 (V) 的 (杂-) 芳基反应以形成式 (VI) 的化合物。然后如果需要，可以任选地将式 (VI) 的化合物脱保护，然后进行环化以形成式 (VII) 的化合物。可以任选地将式 (VII) 的化合物转化为通式 (I) 的化合物。

[0375] 方案 1

[0376]



[0377] 在以上方案中：

[0378] LG_1和 LG_2的每个独立地表示适合的离去基团或官能团；

[0379] X_3和 X_4与它们连接的官能部分一起表示未保护的或受保护的官能团，其在反应（脱保护后）时产生如式 I 中所定义的 X_1；

[0380] E 表示适合的官能团，其可以用于在（杂 -）芳基基团和骨架之间形成直接的键。

[0381] D 表示官能团、诸如 A 或受保护的官能团，其在进一步反应和 / 或脱保护时得到官能团、诸如式 I 中所定义的 A；

[0382] 在以上式（II）化合物与式（III）化合物的反应中，离去基团 LG_1和 LG_2有利地为卤素基团诸如氯或溴基团。该反应可以通过取代反应进行，例如通过在升高的温度例如在回流下、在带有适合的碱例如二异丙基乙胺的有机溶剂诸如乙腈中用式（III）化合物处理式（II）化合物。

[0383] 式（III）化合物可以通过各种选择的保护和脱保护步骤得到。

[0384] 式（IV）化合物可以任选地被适合的保护基团诸如叔丁氧羰基氨基基团以常规方式保护，例如通过在碱性条件下（使用例如三乙胺和 4-（二甲基氨基）吡啶）、在溶剂诸如四氢呋喃中、在升高的温度诸如在回流下用叔丁氧羰基酸酐处理。

[0385] 得到的化合物（IV）与式（V）的（杂 -）芳基化合物的反应在铃木反应条件下（使用例如四（三苯基膦）钯（0）、2- 二环己基膦基 -2’，4’，6’- 三异丙基联苯（Xphos）和磷酸钾）、在混合溶剂诸如 1，4- 二噁烷 / 水中、在升高的温度例如在回流下通过（杂 -）芳基化合物的硼酸 E 或硼酸酯 E 衍生物的偶联有利地进行。

[0386] 可以任选地处理得到的式（VI）的化合物以除去任何需要的保护基团，例如可以将甲硅烷基醚基团、诸如叔丁基二甲基甲硅烷基转化为母体游离羟基。此类脱保护可以以常规方式例如在四氢呋喃中、在室温、使用四丁基氟化铵进行。还可以任选地处理得到的式（VI）的化合物以除去任何需要的保护基团，例如苄基基团可以以常规方式例如使用氢气和活性炭载钯（10％）、在溶剂诸如甲醇中、在诸如室温的温度除去。可以任选地处理式（VI）的化合物以除去任何需要的保护基团，例如可以将叔丁氧羰基氨基基团转化为母体游离氨基基团。此类脱保护可以以常规方式进行，例如通过在酸性条件下（例如使用 4N 乙酰氯溶液）、在溶剂诸如甲醇中、在例如室温进行处理。

[0387] 式（VI）的化合物的环化可以例如在光延反应条件下（使用例如偶氮二甲酸二

异丙酯和三苯基膦）、在混合溶剂诸如 2- 甲基 -1, 4- 二噁烷和甲苯中、在升高的温度诸如 90℃进行。

[0388] 可以任选地处理得到的式 (VII) 的化合物以除去任何需要的保护基团，例如可以将叔丁氧羰基氨基基团转化为母体游离氨基基团。此类脱保护可以以常规方式进行，例如通过在酸性条件下（例如使用在甲醇中的 4N 盐酸溶液）、在室温进行处理。

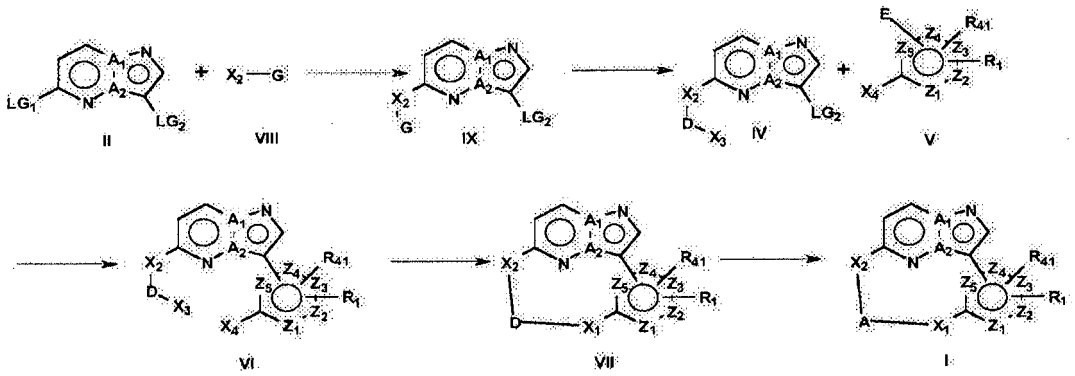
[0389] 可以任选地处理脱保护的化合物以形成式 (I) 的酰胺化合物。所述反应可以有利地通过在室温、在溶剂诸如四氢呋喃中用酰氯和碱诸如三乙胺处理来进行。上述反应还可以使用例如 O-（苯并三唑 -1- 基）-N, N, N', N' - 四甲基脲六氟磷酸盐 (HBTU) 和二异丙基乙胺在溶剂诸如 N, N- 二甲基甲酰胺中、在例如室温进行。

[0390] 可根据方案 1 中描述的合成制备化合物 B19、B21、B76、F81、F82、F83、F84、F86、F87、F88、F89、F91 和 F92。

[0391] 式 (I) 的化合物还可以如以下通用方案 2 中所示制备，其中通过与式 (VIII) 的化合物反应将式 (II) 的吡唑并 [1, 5-a] 嘧啶或咪唑并 [2, 1-f] 哒嗪转化为式 (IX) 的化合物。可以将式 (IX) 的化合物任选地转化为式 (IV) 的化合物，然后将其与式 (V) 的（杂 -）芳基反应，形成式 (VI) 化合物。然后如果需要，可以将式 (VI) 的化合物任选地脱保护，然后进行环化以形成式 (VII) 的化合物。可以任选地将式 (VII) 的化合物转化为通式 (I) 的化合物。

[0392] 方案 2

[0393]



[0394] 在以上方案中：

[0395] LG_1 和 LG_2 的每个独立地表示适合的离去基团或官能团；

[0396] E 表示适合的官能团，其可以用于在（杂 -）芳基基团和骨架之间形成直接的键。

[0397] G 表示适合的官能团或受保护的官能团，其在进一步反应和 / 或脱保护时产生诸如 D 的官能团；

[0398] D 表示官能团、诸如 A 或受保护的官能团，其在进一步反应和 / 或脱保护时产生官能团、诸如式 I 中所定义的 A；

[0399] 在以上式 (II) 化合物与式 (VIII) 的化合物的反应中，离去基团 LG_1 和 LG_2 有利地为卤素基团诸如氯或溴基团。该反应可以通过取代反应进行，例如通过在例如室温、在带有适合的碱例如氢化钠的有机溶剂诸如四氢呋喃中用式 (VIII) 的化合物处理式 (II) 的化合物。

[0400] 式（VIII）的化合物可以商购获得或通过各种选择的保护和脱保护步骤得到。

[0401] 式（IX）的化合物可以使用例如酸性条件诸如在甲醇中的 4N 盐酸溶液、在室温进行脱保护。

[0402] 可以通过使用例如还原性氨基化反应将式（IX）的化合物转化为式（IV）的化合物。该反应可以通过在还原剂诸如三乙酰氧基硼氢化钠和碱诸如三乙胺的存在下、在溶剂诸如二氯甲烷中、在例如室温用醛（alhyde）处理式（IX）的化合物来进行。

[0403] 式（IV）的化合物与式（V）的（杂-）芳基化合物的反应在铃木反应条件下（使用例如四（三苯基膦）钯（0）和磷酸钾）、在混合溶剂诸如 1,4- 二噁烷 / 水中、在升高的温度例如 80℃有利地进行。

[0404] 可以任选地处理得到的式（VI）的化合物以除去任何需要的保护基团，例如可以将甲硅烷基醚基团、诸如叔丁基二甲基甲硅烷基转化为母体游离羟基基团。此类脱保护可以在四氢呋喃中、在例如室温使用例如乙酸进行。可以任选地处理式（VI）的化合物以除去任何需要的保护基团，例如可以将叔丁氧羰基氨基基团转化为母体游离氨基基团。此类脱保护可以以常规方式进行，例如通过在酸性条件下（例如使用 4N 乙酰氯溶液）、在溶剂诸如甲醇中、在例如室温进行处理。

[0405] 通过将羟基与例如亚硫酰氯在碱诸如吡啶的存在下、在溶剂诸如二氯甲烷中、在升高的温度例如在回流下进行反应可以将游离的羟基基团转化为离去基团、诸如氯化物。

[0406] 式（VII）的化合物的环化可以在威廉森（Williamson）反应条件下、使用碱诸如碳酸铯、在溶剂诸如 N,N- 二甲基甲酰胺中、在升高的温度诸如 90℃有利地进行。可以用于式（VII）的化合物的环化的其它的条件可以是，例如通过用 O-（苯并三唑 -1- 基）-N,N,N',N'- 四甲基脲六氟磷酸盐（HBTU）和 N,N- 二异丙基乙胺在溶剂诸如 N,N- 二甲基甲酰胺中、在例如室温进行处理。

[0407] 得到的式（VII）的化合物可以任选地被处理以形成式（I）化合物。

[0408] 可根据方案 2 中描述的合成制备化合物 B74。

[0409] 还可以如下文通用方案 3 中所示制备式（I）的化合物，其中通过与式（VIII）的化合物反应将式（II）的吡唑并 [1,5-a] 嘧啶或咪唑并 [2,1-f] 哒嗪转化为式（IX）的化合物。式（IX）的化合物可以任选地与式（V）的（杂-）芳基反应，形成式（X）的化合物。可以将式（X）的化合物转化为式（XI）的化合物。然后如需要，在环化形成式（VII）的化合物之前可以任选地将式（XI）的化合物脱保护。可以任选地将式（VII）的化合物转化为通式（I）的化合物。

[0410] 在以下方案 3 中：

[0411] LG_1 和 LG_2 的每个独立地表示适合的离去基团或官能团；

[0412] X_4 和 X_5 与它们所连接的官能部分一起表示未保护的或保护的官能团，其在反应时（脱保护后）产生如式 I 中定义的 X_1；

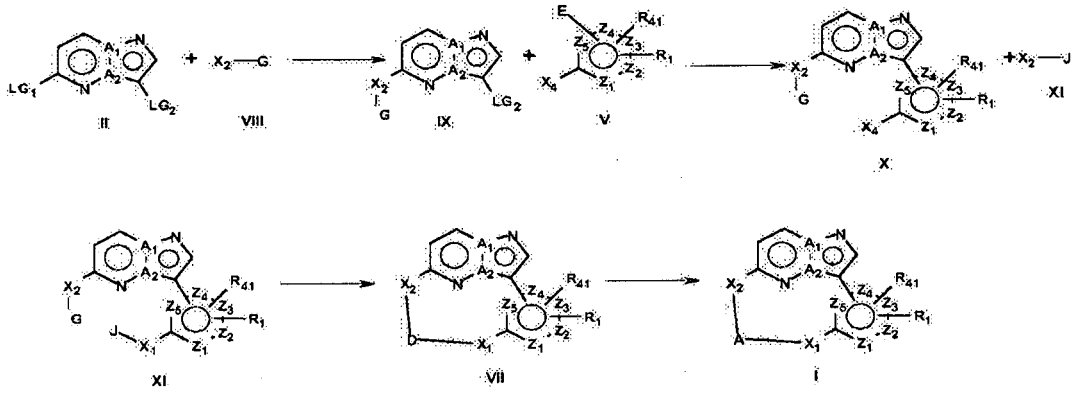
[0413] E 表示可以在（杂-）芳基基团和骨架之间形成直接键的适合的官能团。

[0414] G 和 J 表示官能团或受保护的官能团，其在进一步反应和 / 或脱保护时形成官能团诸如 D；

[0415] D 表示官能团，诸如 A 或保护的官能团，其在进一步反应和 / 或脱保护时形成官能团，诸如式 I 中定义的 A；

[0416] 方案 3

[0417]



[0418] 在以上式 (II) 的化合物与式 (VIII) 的化合物的反应中，离去基团 LG_1和 LG_2有利地是卤素基团、诸如氯或溴基。通过取代反应，例如在有机溶剂诸如乙腈中、与适合的碱（例如二异丙基乙胺）一起、在升高的温度（例如在回流下）用式 (VIII) 的化合物处理式 (II) 的化合物，可以进行所述反应。

[0419] 式 (VIII) 和 (XI) 的化合物可以商购获得或者通过多个选择性保护和脱保护步骤获得。

[0420] 可以任选地用适合的保护基团、诸如叔丁氧羰基氨基基团以常规方式保护得到的式 (IX) 的化合物，例如通过在碱性条件下（使用例如三乙胺和 4-（二甲基氨基）吡啶）、在溶剂诸如四氢呋喃中、在升高的温度（诸如在回流下）用叔丁氧羰基酸酐处理。

[0421] 在铃木反应条件下、使用例如四（三苯基膦）钯 (0)、2- 二环己基膦基 -2',4',6'- 三异丙基联苯 (Xphos) 和磷酸钾、在溶剂混合物诸如 1,4- 二噁烷 / 水中、在升高的温度例如 80℃，通过（杂 -）芳基化合物的硼酸 E 或硼酸酯 E 衍生物的偶联有利地进行得到的 (IX) 的化合物与式 (V) 的（杂 -）芳基化合物的反应。

[0422] 在威廉森条件下、使用碱诸如碳酸钾、在溶剂诸如乙腈中在升高的温度（诸如在回流下）可以有利地进行得到的式 (X) 的化合物与式 (XI) 的化合物的反应。该反应还可以在 Mitsunobu 条件下、使用例如偶氮二甲酸二异丙酯和三苯基膦、在溶剂诸如四氢呋喃中、在升高的温度诸如 90℃进行。

[0423] 可以任选地处理得到的式 (XI) 的化合物以除去任何要求的保护基团，例如可以将叔丁氧羰基氨基基团转化为母体游离氨基基团，且可以将例如酯基基团转化为母体游离羧酸基团。所述脱保护可以以常规方式进行，例如通过在酸性条件下、例如使用 6N 盐酸水溶液、在溶剂诸如乙腈中、在升高的温度例如 60℃或使用酸诸如三氟乙酸、在溶剂诸如二氯甲烷中、在例如室温进行处理。

[0424] 式 (XI) 的化合物的环化可以例如通过在溶剂诸如 N,N- 二甲基甲酰胺中、在例如室温用 O-（苯并三唑 -1- 基）-N,N,N',N'- 四甲基脲六氟磷酸盐 (HBTU) 和 N,N- 二异丙基乙胺处理来进行。

[0425] 可以任选地处理得到的式 (VII) 的化合物，形成式 (I) 的化合物。

[0426] 可以根据方案 3 中描述的合成来制备化合物 B36、B48、F105、F106 和 F108。

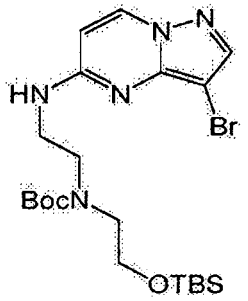
[0427] 通过专利申请 WO2013/045653 A1 和 WO2013/046029 A1 中记载的具体方法阐述以

上的通用方法。

[0428] 中间体 F78 的制备

[0429] 根据通用方案 1 制备中间体 F78。

[0430]

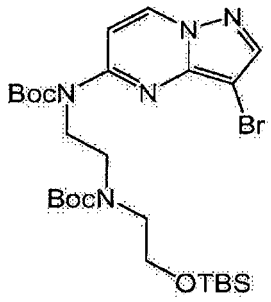


[0431] 步骤 A

[0432] 将 3- 溴 -5- 氯吡唑并 [1,5-a] 嘧啶 (14.0g,60.22mmol,1 当量)、连接基 (其合成记载于专利 WO2013/045653 A1 中间体 21 的制备中)(21.1g,66.24mmol,1.1 当量) 和 DIPEA(13.67ml,78.29mmol,1.3 当量) 在乙腈 (180ml) 中的溶液在 70/80℃加热 18 小时。在通过 TLC 板监测完成时,将该反应混合物浓缩。将残余物溶于 EtOAc 中,用水洗涤 2 次,并用盐水洗涤 1 次。将有机层干燥 (MgSO4),过滤,浓缩。将粗制的产物经快速色谱进一步纯化,使用洗脱剂梯度洗脱 : 庚烷 :EtOAc 100:0 至 80:20(快速) 至 60:40(慢速)。收集产物级分,并浓缩,得到 23.6g 棕色固体 (76% 收率)。

[0433] MH+:514.2/516.2

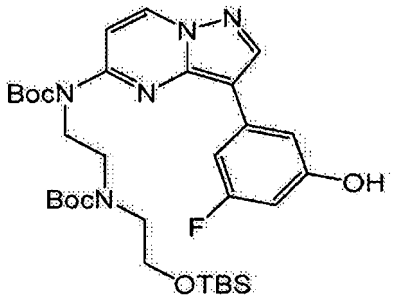
[0434]



[0435] 步骤 B

[0436] 将来自步骤 A 的标题化合物、Boc 酸酐 (15.01g,68.8mmol,1.5 当量) 和 DMAP(0.28g,2.29mmol,0.05 当量) 溶于 THF(137ml) 中,并将该混合物在 65℃加热 4 小时。在通过 TLC 监测完成时,将该反应混合物浓缩。将粗制的产物经快速色谱进一步纯化,使用洗脱剂梯度 : 庚烷 :EtOAc 100:0 至 50:50,快速,6 个柱体积。收集产物级分,并浓缩,得到 27.0g 棕色油状物 (96% 收率)。

[0437]



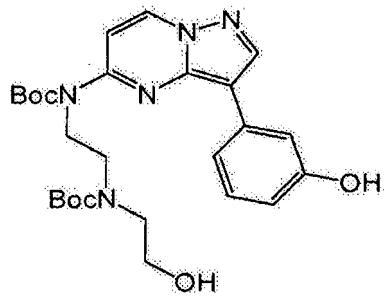
[0438] 步骤 C

[0439] 将来自步骤 B 的标题化合物、(3- 氟 -5- 羟基苯基) 硼酸 (1.78g,11.39mmol,1.0 当量)、XPhos(0.32g,0.68mmol,0.06 当量) 和磷酸钾 (7.2g,33.92mmol,3.0 当量) 的混合物溶于二噁烷 / 水 3:1 中,并用 N2 脱气。然后将四钯 (Palladium Tetrakis)(0.39g,0.34mmol,0.03 当量) 加入该搅拌的溶液中。将得到的反应混合物在 80℃在 N2 气氛下搅拌 6 小时。为了完成反应,加入另外的量的硼酸 (1.0 当量)、四钯 (0.03 当量) 和 XPhos(0.06 当量)。将该反应混合物在 90℃再搅拌 18 小时。

[0440] 将该混合物用 EtOAc 稀释,并将各层分离。将有机层用水洗涤 2 次,并用盐水洗涤 1 次,干燥 (MgSO4),过滤,浓缩。将粗制的产物经快速色谱进一步纯化,使用洗脱剂梯度洗脱 : 庚烷 :EtAOc。100:0 至 60:40。收集产物级分,并浓缩,得到 7.2g 固体 (98% 收率)。

[0441] MH+:546.3

[0442]

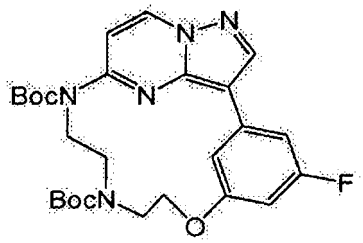


[0443] 步骤 D

[0444] 向来自步骤 C 的标题化合物在 THF(33ml) 中的溶液中加入 TBAF1M 在 THF 中的溶液 (14.5ml,14.5mmol)。将该反应混合物在室温搅拌 18 小时,然后将溶剂浓缩至干燥。将残余物溶于乙酸乙酯中,用水洗涤 3 次,并用盐水洗涤 1 次。将有机层经硫酸镁干燥,过滤,浓缩。将粗制的产物经快速色谱 (n-Hp:EA 0:20 至 30:70) 进一步纯化,得到标题化合物,为白色固体 (5.0g,84% 收率)。

[0445] MH+:432.2

[0446]

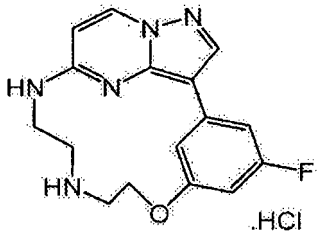


[0447] 步骤 E

[0448] 在 90℃历经 5 小时向三苯基膦 (7.66g,29.22mmol) 在甲苯 (44ml) 中的搅拌的溶液中同时加入来自步骤 D 的标题化合物 (5.0g,9.74mmol) 在 2-MeTHF(11.6ml) 中的溶液和 DIAD(5.79ml,29.22mmol) 在甲苯 (11.6ml) 中的溶液。将得到的混合物在 90℃进一步搅拌 30 分钟。将该反应混合物浓缩至干燥,并未经纯化地直接用于下一个步骤。

[0449] MH+:514.3

[0450]



[0451] 步骤 F

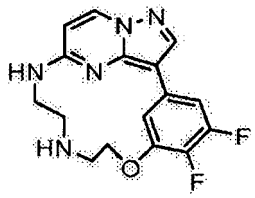
[0452] 向来自步骤 E 的标题化合物 (9.8g,19.08mmol) 中加入 4M HCl 在 MeOH(57ml) 中的溶液。将得到的混合物在室温搅拌 18 小时,然后在 40℃搅拌 8 小时。在室温将该白色浆体过滤掉,并用二异丙基醚洗涤。将固体在真空下干燥,得到标题化合物,为白色固体 (3.0g,88%收率,历经 2 步骤)。

[0453] 熔点 :>300℃,分解

[0454] MH+:314.10

[0455] 中间体 F79 的制备

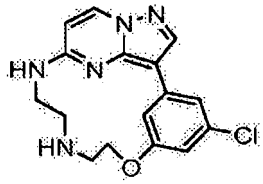
[0456]



[0457] 根据通用方案 1 并根据专利申请 WO2013/045653 A1 中记载的得到实施例 17 的程序来制备。

[0458] 中间体 F80 的制备

[0459]



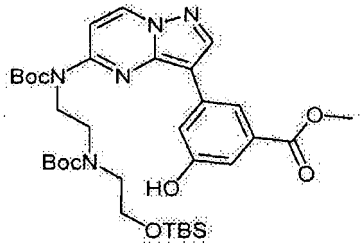
[0460] 根据通用方案 1 并根据专利申请 WO2013/045653 A1 中记载的得到实施例 17 的程序来制备。

[0461] 根据通用方案 1 并根据专利申请 WO2013/045653 A1 中记载的得到实施例 6 的程序来制备实施例 F81 至 F89。

[0462] 中间体 F90 的制备

[0463] 根据通用方案 1 制备中间体 F90

[0464]

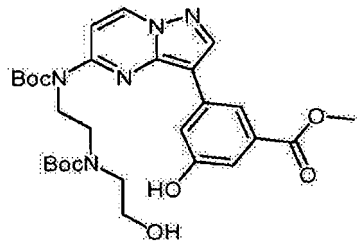


[0465] 步骤 A

[0466] 将二噁烷和水 (3:1)(148ml) 的混合物置于烧瓶中，并通过通入氮气脱气。然后加入来自实施例 F78、步骤 B 的标题化合物 (15g,24.4mmol,1.0 当量)、硼酸酯 (8.82g,31.73mmol,1.3 当量)、四钯 (.568g,0.49mmol,0.02 当量)、XPhos(0.93g,1.95mmol,0.08 当量) 和磷酸钾 (25.9g,5.0 当量)，并将该混悬液在 85℃在氮气下搅拌 15 小时。在通过 LCMS 监测完成时，除去二噁烷，加入水，并将产物用乙酸乙酯萃取。将有机层经硫酸镁干燥，过滤，并将滤液减压浓缩。将产物经硅胶快速色谱使用庚烷：乙酸乙酯的洗脱剂混合物 (0%至 33%的乙酸乙酯) 纯化。收集产物级分，并将溶剂蒸发至干燥。得到标题化合物，为固体 (13.43g,80.2%收率)。

[0467] MH+:586.1

[0468]



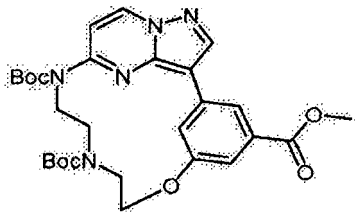
[0469] 步骤 B

[0470] 将来自步骤 C 的标题化合物和 1M TBAF(21.54ml,1 当量) 在 THF(59ml) 中的溶液在室温搅拌 1 小时。在通过 LCMS 监测完成时，减压除去溶剂，并将残余物溶于乙酸乙酯中，用水 (x3) 和盐水洗涤。将有机层用盐水洗涤，经硫酸镁干燥，并蒸发至干燥。将产物原样

用于下一个反应步骤中。

[0471] MH+:572.0

[0472]



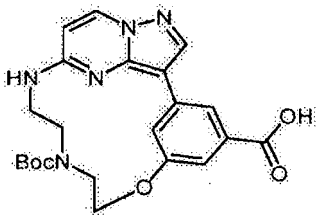
[0473] 步骤C

[0474] 分两批次平行进行该反应。

[0475] 在90℃用3小时将来自步骤D的标题化合物(8.95g,15.65mmol)在2-甲基THF(20ml/mmol)中的溶液和DIAD(9.31ml,46.95mmol,3.0当量)在甲苯(同体积)中的溶液同时加入三苯基膦(12.31g,46.95mmol,3.0当量)在甲苯(75 ml/mmol起始物A)中的溶液中。随后,将该反应混合物加热30分钟。在通过LCMS监测完成时,蒸发溶剂,并将产物经硅胶快速色谱纯化,使用作为洗脱剂混合物的二氯甲烷:甲醇(0%至10%甲醇)。收集产物级分,并将溶剂蒸发至干燥,得到7.7g期望化合物,88%收率。

[0476] MH+:554.0

[0477]



[0478] 步骤D

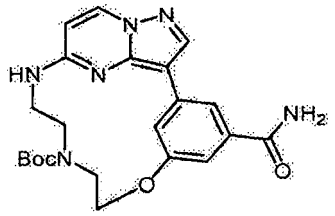
[0479] 将来自步骤E的标题化合物(1.5g,2.71mmol,1.0当量)和氢氧化锂水合物(0.34g,8.13mmol,3.0当量)的混合物混悬于THF/MeOH/H2O(2:2:1)(25ml)中。将该混合物在50℃搅拌15小时。在通过LCMS监测完成时,除去溶剂。加入水,并加入HCl 1M以将溶液酸化至pH 6。将得到的固体过滤,并用甲醇洗涤,然后在高真空下干燥(615mg)。

[0480] 将水相中的产物用二氯甲烷萃取。将有机层经硫酸镁干燥,过滤,并将滤液减压浓缩。将产物经硅胶快速色谱纯化,使用作为洗脱剂混合物的DCM:MeOH(0%至100%甲醇),然后用二氯甲烷:甲醇(0至10%甲醇)。

[0481] 得到标题化合物,为白色固体(917mg,77%收率)

[0482] MH+:440.0

[0483]

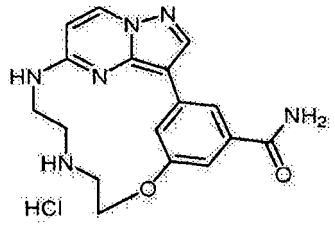


[0484] 步骤 E

[0485] 将 HBTU(0.637g,1.68mmol,1.2 当量）加入至来自步骤 F 的标题化合物 (0.615mg,1.40mmol,1.0 当量）、氯化铵 (0.08g,1.40mmol,1.10 当量）和 DIPEA(0.595ml,3.50mmol,2.5 当量）在 DMF(4ml) 中的溶液中。将该混合物在室温搅拌 19 小时。在通过 LCMS 监测完成时，将该反应混合物用乙酸乙酯稀释，并用 NaHCO3 饱和溶液洗涤。将有机层经硫酸镁干燥，过滤，并将滤液减压浓缩。将产物经硅胶快速色谱纯化，使用作为洗脱剂混合物的庚烷：乙酸乙酯 (0%至 100%乙酸乙酯）。收集产物级分，并将溶剂蒸发至干燥，得到标题化合物，为固体 (507mg,82%）。

[0486] MH+:439.0

[0487]



[0488] 步骤 F

[0489] 将来自步骤 G 的标题化合物 (507mg,1.16mmol,1.0 当量）在二噁烷中的 4M HCl(3.5ml) 中在室温搅拌 3 小时。在通过 LCMS 监测完成时，除去溶剂。加入乙醚，并将形成的固体过滤掉，并在真空下干燥，得到标题化合物，为白色固体 (372mg,85%）。

[0490] MH+:339.0

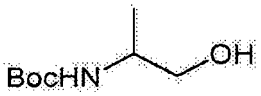
[0491] HPLC 保留时间 :0.197 分钟

[0492] 熔点：

[0493] 根据通用方案 1 并根据专利申请 WO2013/045653 A1 中记载的得到实施例 6 的程序制备实施例 F91 至 F92。

[0494] 中间体 F104 的制备

[0495]



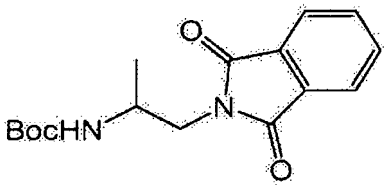
[0496] 步骤 A

[0497] 将 Boc 酸酐 (15.98g,73.23mmol,1.1 当量）加入至 2-氨基丙 -1- 醇 (5.0g,66.57mmol,1.0 当量）在 CH2Cl2(200ml) 中的溶液中。将该混合物在室温搅拌 1 小时。在通过 TLC 监测完成时，将产物经硅胶快速色谱纯化，使用作为洗脱剂混合物的庚烷：乙酸乙

酯（0%至50%乙酸乙酯）。收集产物级分，并将溶剂蒸发至干燥，得到10.89g标题化合物（93%收率）。

[0498] MH+:198.1(M+H+Na)

[0499]

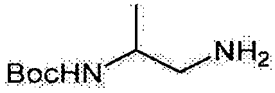


[0500] 步骤B

[0501] 将来自步骤A的标题化合物（10.89g,62.13mmo,1.0当量）和邻苯二甲酰亚胺（13.71g,93.2mmol,1.5当量）溶于无水THF(167 ml)中。将该反应混合物脱气，并加入三苯基膦（24.44g,93.2mmol,1.5当量）。将该反应混合物在N2气氛下冷却至0℃。用20 ml THF稀释的DIAD(18.84g,93.19mmol,1.5当量)，并逐滴添加（放热）。当添加完成时，使该反应达到室温，并搅拌90分钟。在通过LCMS监测完成时，除去溶剂，加入乙腈，加热直至溶解完成，然后冷却。将由此形成的固体过滤，并在真空下干燥，得到7.68g第一级分。

[0502] 将母液中的产物经硅胶快速色谱纯化，使用作为洗脱剂混合物的庚烷：乙酸乙酯（0%至50%乙酸乙酯）。收集产物级分，并将溶剂蒸发至干燥，得到7.892g固体状的标题化合物。其包含与DIAD有关的相同杂质。

[0503]



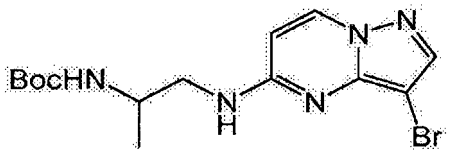
[0504] 步骤C

[0505] 将来自步骤B的标题化合物（9.0g,29.57mmol,1.0当量）和水合肼（2.76ml,88.71mmol,3.0当量）在乙醇（89ml）中的溶液在70℃搅拌4小时。在通过LCMS监测完成，将该反应混合物冷却至室温；将得到的混悬液过滤以除去形成的白色固体。然后将滤液蒸发，并将残余物溶于乙酸乙酯中，用NaOH 1M和盐水洗涤。将有机层干燥，过滤，并浓缩，得到标题化合物，为无色油状物，将其原样用于下一合成步骤中。

[0506] 实施例F105

[0507] 根据通用方案3制备实施例F105

[0508]



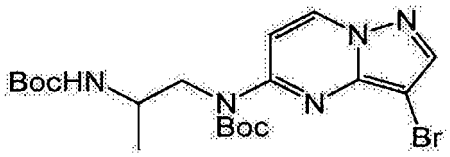
[0509] 步骤A

[0510] 将3-溴-5-氯吡唑并[1,5-a]嘧啶（3.0g,12.9mmol,1.0当量）、中间体F104(4.49g,25.8mmol,2.0当量）和DIPEA(4.61ml,27.09mmol,2.1当量）在乙腈（39ml）中的溶液回流15小时。在通过LCMS监测完成时，除去溶剂。加入乙酸乙酯，并用水洗涤。

将有机层经硫酸镁干燥，过滤，并将滤液减压浓缩。将产物经硅胶快速色谱纯化，使用作为洗脱剂混合物的庚烷：乙酸乙酯（0％至66％乙酸乙酯）。收集产物级分，并将溶剂蒸发至干燥，得到4.04g固体状的标题化合物（84.5％收率）。

[0511] MH+:370.1/372.1

[0512]

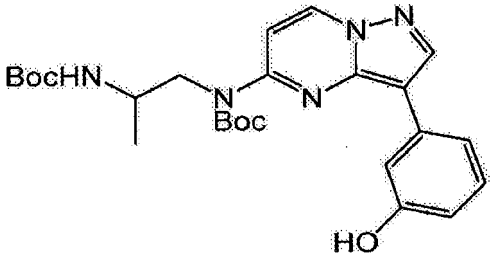


[0513] 步骤B

[0514] 将Boc酸酐（2.59g,11.86mmol,1.1当量）加入至来自步骤A的标题化合物（3.99g,10.78mmol,1.0当量）、三乙胺（1.79ml,12.94mmol,1.2当量）和DMAP(66mg,.54mmol,0.05当量）在THF(32ml)中的混合物中。将该溶液回流150分钟。在通过LCMS监测完成时，除去溶剂。加入水，并将产物用乙酸乙酯萃取。将有机层经硫酸镁干燥，过滤，并将滤液减压浓缩。将产物经硅胶快速色谱纯化，使用作为洗脱剂混合物的庚烷：乙酸乙酯（5％至40％乙酸乙酯）。收集产物级分，并将溶剂蒸发至干燥，得到4.63g标题化合物（91％收率）。

[0515] MH+:492.1/494.1

[0516]

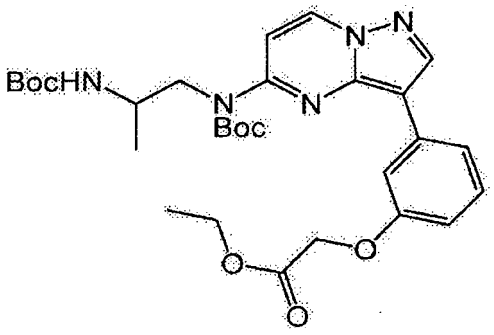


[0517] 步骤C

[0518] 将二噁烷和水（3:1）的混合物（126ml）置于烧瓶中，并通过通入氮气脱气。然后加入来自步骤B的标题化合物（4.63g,9.84mmol,1.0当量）、3-羟基苯基硼酸（1.76g,12.79mmol,1.3当量）、四钯（228mg,0.197mmol,0.02当量）、XPhos(377mg,0.79mmol,0.08当量）和磷酸钾（0.223g,49.2mmol,5.0当量），并将该混悬液在85℃在氮气下搅拌3小时。在通过LCMS监测完成时，除去二噁烷。加入水，并将产物用乙酸乙酯萃取。将有机层经硫酸镁干燥，过滤，并将滤液减压浓缩。将产物经硅胶快速色谱纯化，使用作为洗脱剂混合物的二氯甲烷：甲醇（100:0至20:1）。收集产物级分，并将溶剂蒸发至干燥，得到4.39g标题化合物（92％收率）。其包含一些OPPH3。

[0519] MH+:484.3

[0520]

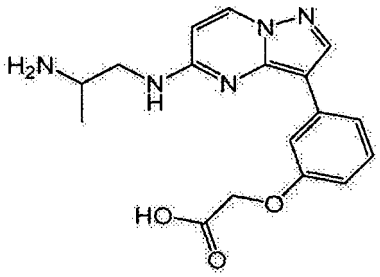


[0521] 步骤 D

[0522] 将来自步骤 C 的标题化合物（1.5g，3.1mmol，1.0 当量）、2- 溴乙酸乙酯（514ul，4.65mmol，1.5 当量）、碳酸钾（857mg，6.2mmol，2.0 当量）和碘化钾（27mg，0.16mmol，0.05 当量）的混合物在 80℃在 DMF（9.3ml）中加热 2 小时。在通过 LCMS 监测完成时，加入水，并将产物用乙酸乙酯萃取。将有机层经硫酸镁干燥，过滤，并将滤液减压浓缩。将产物经硅胶快速色谱纯化，使用作为洗脱剂混合物的庚烷：乙酸乙酯（5％至 33％乙酸乙酯）。收集产物级分，并将溶剂蒸发至干燥，得到 1.31g 标题化合物（74％收率）。

[0523] MH+：592.3

[0524]

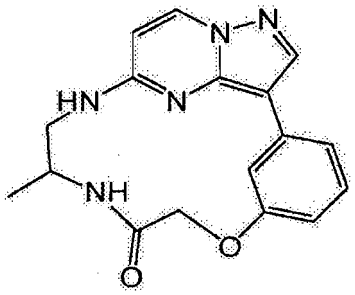


[0525] 步骤 E

[0526] 向来自步骤 D 的标题化合物（1.31g，2.29mmol，1.0 当量）在 THF（12 ml/mmol）（6.87ml）中的溶液中加入 HCl 6M（12 ml/mmol）。将该混合物在 60℃在密封管中搅拌 3 小时。在通过 LCMS 监测完成时，除去溶剂。加入甲苯 /THF（1:1），并蒸发。然后加入甲苯，蒸发，最后加入乙醇，并蒸发。将粗制物在真空下干燥，并原样用于下一个反应步骤。

[0527] MH+：342.2

[0528]



[0529] 步骤 F

[0530] 在室温用3小时将来自步骤E的标题化合物(2.02mmol)和DIPEA(1.72ml,10.1mmol,5.0当量)在DMF(60ml)中的混悬液滴加至HATU(2.3g,6.06mmol,3.0当量)和DIPEA(5.15ml,30.3mmol,15.0当量)在DMF(40ml)中的溶液中。在通过LCMS监测完成时,加入在甲醇中的7N氨,并搅拌30分钟。除去溶剂,并将产物经硅胶快速色谱纯化,使用作为洗脱剂混合物的二氯甲烷:甲醇(100:0至20:1)。收集产物级分,并将溶剂蒸发至干燥。使用乙腈将纯的产物沉淀,并在真空下干燥,得到463mg苍白色固体(71%收率)。

[0531] MH+:324.2

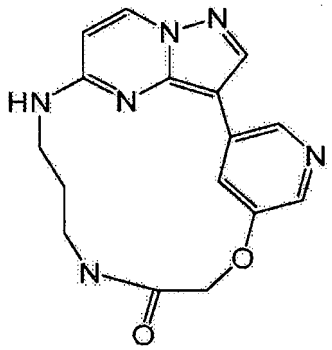
[0532] 保留时间:2.107分钟

[0533] 熔点:>300℃。

[0534] 实施例F106

[0535] 根据通用方案3且更精确地以与实施例F105类似的程序制备实施例F106。

[0536]



[0537] 收率:5mg,2.9%

[0538] MH+:325.2

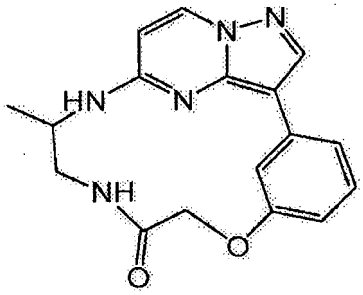
[0539] 保留时间:1.343分钟

[0540] 熔点:ND

[0541] 中间体F107的制备

[0542] 根据通用方案3制备中间体F107

[0543]



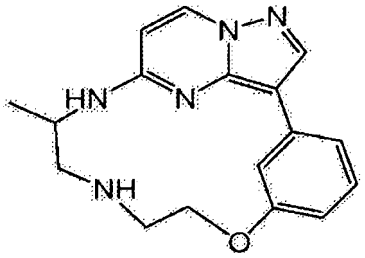
[0544] 根据与实施例F129类似的程序制备标题化合物。

[0545] MH+:324.2

[0546] 实施例F108

[0547] 根据通用方案3制备实施例F108

[0548]



[0549] 步骤 A

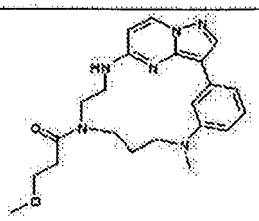
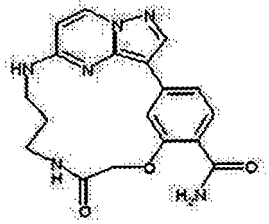
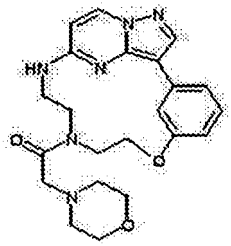
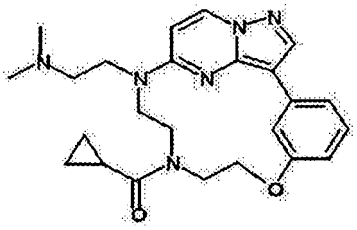
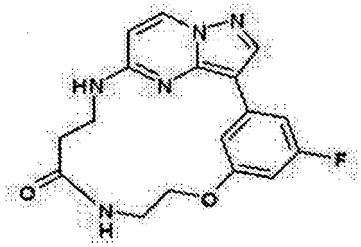
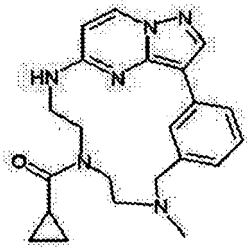
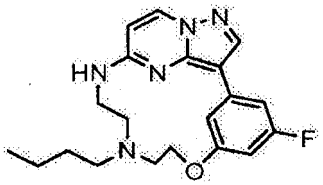
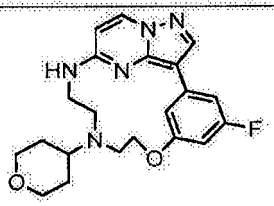
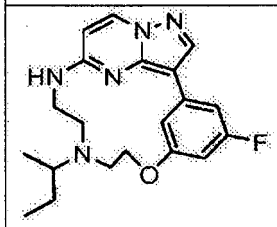
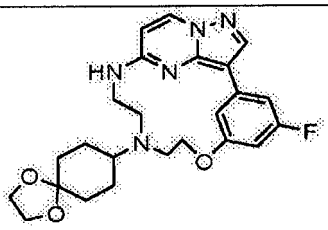
[0550] 将中间体 F107(163mg,0.5mmol,1.0 当量）溶于在 THF 中的 2M 硼烷二甲基硫醚(0.38ml,5.0mmol,10.0 当量）和 THF(1.5ml）中，产生气体。将该反应混合物在室温搅拌 32 小时。在通过 LCMS 监测完成时，将该反应混合物用 2N HCl 淬灭，并在 100℃加热 1 小时(THF 蒸发）。将产物用 DCM 萃取 2 次，并用 DCM:MeOH 9:1 萃取一次。将合并的有机层浓缩。将粗制物经快速色谱使用 DCM:MeOH 98:2 至 95:5 的混合物（慢速）纯化。将该化合物经 PREP HPLC 进一步纯化，得到 47mg 标题化合物（30％收率）。

[0551] MH+:310.2

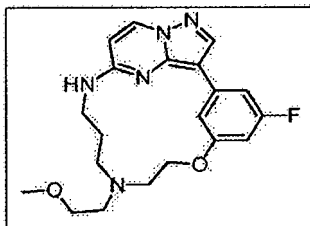
[0552] 保留时间 :1.952

[0553] 表 1

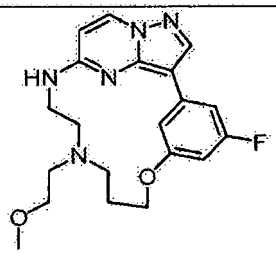
[0554]

 化合物 B19，实施例 B16	 化合物 B21，实施例 B61
 化合物 B36，实施例 B23	 化合物 B48，实施例 B35
 化合物 B74，实施例 B63	 化合物 B76，实施例 B65
 化合物 F81，实施例 F81	 化合物 F82，实施例 F82
 化合物 F83，实施例 F83	 化合物 F84，实施例 F84

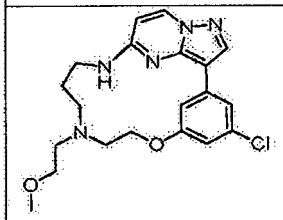
[0555]



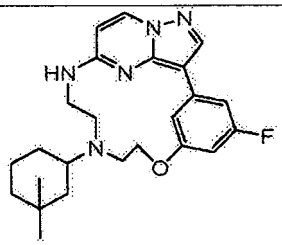
化合物 F86，实施例 F86



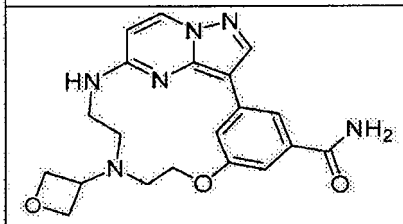
化合物 F87，实施例 F87



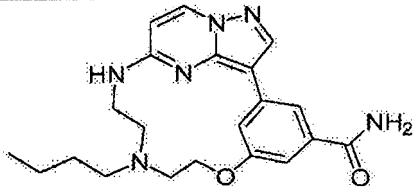
化合物 F88，实施例 F88



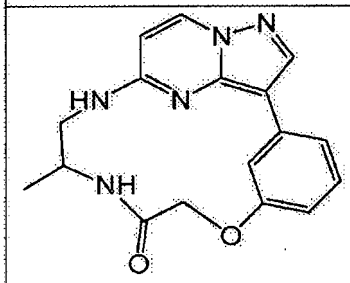
化合物 F89，实施例 F89



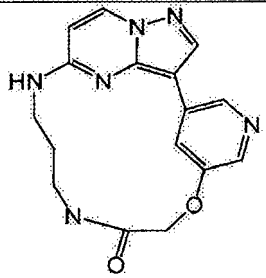
化合物 F91，实施例 F91



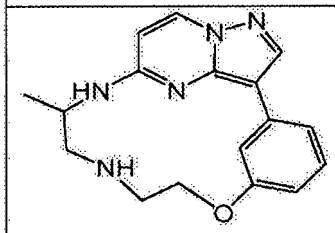
化合物 F92，实施例 F92



化合物 F105，实施例 F105



化合物 F106，实施例 F106



化合物 F108，实施例 F108

[0556] 根据 WO2013/045653 A1 和 WO2013/046029 A1 中记载的分析方法和分析结果鉴定化合物。

[0557] 表 2：熔点

[0558]

化合物 N°	熔点（℃）
F81	370.2
F82	398.4
F83	370.4
F84	454.3
F86	386.2
F87	386.2
F88	402.1
F89	423.3
F91	395.2
F92	395.2
F105	324.2
F106	325.2
F108	310.2

[0559] 表 3:LCMS 数据

[0560]

化合物编号	质量 (MH)+峰	保留时间（分钟）	LCMS 方法
F81	370.2	2.549	2
F82	398.4	2.297	2
F83	370.4	2.385	2
F84	454.3	2.410	2
F86	386.2	2.083	2
F87	386.2	2.131	2
F88	402.1	2.252	2

[0561]

F89	423.3	2.942	2
F91	395.2	1.789	2
F92	395.2	1.633	2
F105	324.2	2.107	2
F106	325.2	1.343	2
F108	310.2	1.952	2

[0562] 在体外基于肽的激酶测定中使用 RIP2 重组蛋白质评估 RIP2 激酶的抑制。

[0563] B 激酶活性测定

[0564] 在体外基于肽的激酶测定中使用 RIP2 重组蛋白质评估 RIP2 激酶的抑制。

[0565] 方案

[0566] 使用放射性测量的蛋白激酶测定（^{33}Pan Qinase® 活性测定）测定激酶活性。所有的测定在来自 PerkinElmer 的 96- 孔 FlashPlates™ 上以 50 μl 反应体积进行。以如下顺序的四个步骤吸量反应混合物：

[0567] 10 μl 非放射的 ATP 溶液（在 H2O 中）

[0568] 25 μl 测定缓冲液 /[γ-^{33}P]-ATP 混合物

[0569] 5 μl 在 10% DMSO 中的测试样品

[0570] 10 μl 酶 / 底物混合物

[0571] 用于 RIP2 的测定包含 70 mM HEPES-NaOH pH 7.5、3 mM $MgCl_2$、3 mM $MnCl_2$、3 μM 正钒酸钠、1.2 mM DTT、50 μg/ml PEG20000、ATP(3.0 μM)、[γ-^{33}P]-ATP（约 5 x 10^{05} cpm/孔）、蛋白激酶 RIP2(15.7 nM) 和底物 (RBER-Chktide)、2.0 μg/50 μl)。

[0572] 将该反应混合物在 30℃温育 60 分钟。使用 50 μl 2% (v/v)H_3PO_4 停止反应，对板进行抽气，并用 200 μl 0.9% (w/v)NaCl 洗涤两次。使用微孔板闪烁计数器测定 ^{33}Pi 的掺入（计算“cpm”）。

[0573] 化合物

[0574] 将化合物溶于 10 mM DMSO 中。当需要时，在浴声波仪中对该溶液声波处理。

[0575] 表 4 提供了使用上文提及的激酶测定获得的本发明化合物的两个浓度（1 μM 和 0.1 μM) 时的 pIC_{50} 值和保留活性值百分比。

[0576] 表 4

[0577]

化合物编号	RIP2 的 IC_{50}	1 μM 的保留 RIP2 活性百分比	0.1 μM 的保留 RIP2 活性百分比
B19		**	**
B21	+++	**	**
B36	+++	**	**
B48	+++	**	**
B74	++	**	**
B76	++	**	*
F81	+++	**	**
F82	+++	**	**
F83	+++	**	**
F84	++	**	**
F86	+++	**	**
F87	+++	**	**
F88	+++	**	**
F89	++	**	**
F91	+++	**	**
F92	+++	**	**
F105	++	**	*
F106	++	ND	ND
F108	++	ND	ND

[0578] + 表示 IC50>1 μM，++ 表示 100 nM 至 1 μM 之间的 IC50，且 +++ 表示 IC50<100nM

[0579] * 表示超过 50％的保留激酶活性百分比，** 表示低于 50％的保留激酶活性百分比

[0580] ND ＝未测定