SUBSTITUTED BICYCLIC HETEROCYCLES AS MALT-1 INHIBITORS

CROSS REFERENCE TO RELATED APPLICATION

This application claims priority to Indian Patent Provisional application number 202241002859 that was filed on 18th January 2022. The entire contents of this provisional application are hereby incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof which is useful as a MALT-1 inhibitor and for the treatment of diseases or disorders dependent on MALT-1. The present invention also relates to a preparation method of compounds of formula (I), pharmaceutical compositions comprising them and their uses as therapeutic agents for the treatment of diseases, particularly cancer and autoimmune diseases.

BACKGROUND OF THE INVENTION

MALT-1 (mucosa associated lymphoid tissue lymphoma translocation protein 1) is an intracellular signalling protein, known from innate (natural killer cells NK, dendritic cells DC and mast cells) and adaptive immune cells (T cells and B cells). MALT-1, in association with BCL10 and CARD11, functions as a scaffolding protein to activate the inhibitor of IκB kinase (IKK) complex. The function of MALT-1 is best known in the context of T cell receptor (TCR) signalling, where it mediates nuclear factor κB (NF-κB) signalling leading to control of lymphocyte activation, survival and differentiation (S. Hailfinger et al., Immunol. Rev., 232 (2009), pp. 334-347, M. Thome, Nat. Rev. Immunol., 8 (2008), pp. 495-500). In addition to its scaffolding function, MALT-1 is the only gene encoding a paracaspase that belongs to the caspase (cysteine-aspartic proteases) family of proteases that displays high homology to caspases from mammals and metacaspases from plants and fungi (A.G. Uren et al., Mol. Cell, 6 (2000), pp. 961-967). The paracaspase MALT-1 plays an essential role in the activation of immune cells by specific subtypes of immune receptors, which induce nuclear translocation of the NF-κB transcription factor complex leading to the activation of the NF-κB signalling pathway (M. Jaworski et al., Cell Mol. Life Science 2016, 73, 459-473). NF-κB target genes include cytokines and anti-apoptotic proteins, which together promote the activation, proliferation and survival of the activated immune cells upon receptor triggering and thereby allow the efficient generation of an immune response.

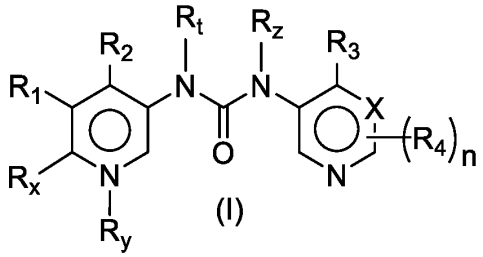
Studies in BCL10 and MALT 1-deficient mice seem to suggest their essential role in the signalling cascade from the antigen receptors to the transcription factor NF-kB. Moreover, chromosomal translocations leading to overexpression of BCL10 and MALT-1 or creating the constitutively active fusion protein API2-MALT-1, appear to result in an uncontrolled and stimulus-independent activation of NF-kB. Inhibitors of the proteolytic activity of MALT-1 have been described with activity in preclinical lymphoma models (M. Vincendeau et al. Int. J. Hematol. Oncol. 2013, 2, 409-417). Moreover, certain publications appear to suggest the important role of MALT-1 and its proteolytic function in signaling cascades triggered by innate cell receptors like Dectin receptors and in signaling cascades triggered by G-protein coupled receptors in many cell types.

International applications WO2015181747, WO2017081641, WO2018020474, WO2018119036, WO2018141749, WO2018165385, WO2018226150, WO2020010252, WO2020111087, WO2021000855 and WO2020208222 report several small molecule compounds and their derivatives capable of targeting MALT-1 and thereby inhibiting the activity of MALT-1. However, there is a need for the development of small molecule MALT-1 inhibitors with the potential to dampen NF-kB signalling in various proliferative disorders and autoimmune diseases.

SUMMARY OF THE INVENTION

Provided herein is a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof and pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof that are useful as MALT-1 inhibitors and for the treatment of diseases or disorders dependent on or mediated by MALT-1. The present invention also provides a preparation of a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

In one aspect, the present invention provides a compound of formula (I):



(I)

or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof; wherein,

X represents N or C;

R_x and R_y combine together with the atoms to which they are attached to form a fused 5-membered heteroaryl substituted with 1 or 2 occurrence(s) of R_6;

R_t and R_z independently represents hydrogen or alkyl;

R_1 is hydrogen, halogen, cyano, hydroxy, amino, alkoxy, alkyl or haloalkyl;

R_2 is hydrogen, halogen, alkyl or haloalkyl;

R_3 is aryl, cycloalkyl, heterocyclyl or a group represented by a formula $-CHR_aR_b$; wherein the aryl, cycloalkyl and heterocyclyl are optionally substituted with 1, 2 or 3 substituent(s) independently selected from halogen, hydroxy, haloalkyl and alkyl;

R_a and R_b independently represent hydrogen, alkyl, alkoxy, alkoxy-alkyl, haloalkyl or cycloalkyl;

R_4 at each occurrence is independently hydrogen, halogen, alkyl, alkoxy, haloalkyl, haloalkoxy or cycloalkyl; or any two adjacent R_4 groups combine together with the atoms to which they are attached to form a fused 5-membered heteroaryl substituted with 1 or 2 occurrence(s) of R_5;

R_5 at each occurrence is independently hydrogen, alkyl, halogen, haloalkyl, cyano, alkoxy, haloalkoxy, amino, aryl, cycloalkyl, heterocycloalkyl or heteroaryl;

R_6 at each occurrence is independently hydrogen, halogen, hydroxy, cyano, alkoxy, alkyl or cycloalkyl; wherein the alkyl is optionally substituted with 1 to 3 substituent(s) independently selected from hydroxy, oxo, halogen, alkylamino, alkoxy and heterocycloalkyl; and

n is 1, 2 or 3.

In another aspect, the present invention provides the preparation of a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

In yet another aspect, the present invention provides a pharmaceutical composition comprising the compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof and at least one pharmaceutically acceptable excipient (such as a pharmaceutically acceptable carrier or diluent).

In another aspect, the present invention provides a pharmaceutical composition comprising the compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof for use as a medicament.

In another aspect, the present invention provides a pharmaceutical composition comprising the compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof for use in treating or preventing of a disease or disorder mediated by MALT-1.

In another aspect, the present invention provides a pharmaceutical composition comprising the compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof for treating diseases or disorders associated with MALT-1 including mutations and overexpression thereof.

In another aspect, the present invention provides a method of treating a disease or disorder mediated by the inhibition of MALT-1, in a subject comprising administering to the subject in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof. The disease or disorder dependent upon MALT-1 is cancer.

In another aspect, the present invention provides a use of a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof in the manufacture of a medicament for treating a disease or disorder mediated by MALT-1, e.g., cancer.

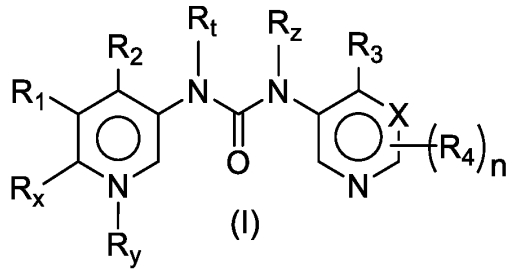
DETAILED DESCRIPTION OF THE INVENTION

The present invention provides substituted bicyclic heterocyclic compounds, referred as a compound of formula (I), which are useful as MALT-1 inhibitors and for the treatment of diseases or disorders dependent on or mediated by MALT-1. The present invention further provides pharmaceutical composition comprising the said compound or a stereoisomer or a tautomer thereof.

Each embodiment is provided by way of explanation of the invention and not by way of limitation of the invention. In fact, it will be apparent to those skilled in the art that various modifications and variations can be made to the compounds, compositions and methods described herein without departing from the scope or spirit of the invention. For instance, features illustrated or described as part of one embodiment can be applied to another embodiment to yield a still further embodiment. Thus, it is intended that the present invention includes such modifications and variations and their equivalents. Other objects, features and aspects of the present invention are disclosed in or are obvious from, the following detailed

description. It is to be understood by one of ordinary skill in the art that the present discussion is a description of exemplary embodiment only and is not to be construed as limiting the broader aspects of the present invention.

In one embodiment, the present invention provides a compound of formula (I):



(I)

or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof; wherein,

X represents N or C;

R_x and R_y combine together with the atoms to which they are attached to form a fused 5-membered heteroaryl substituted with 1 or 2 occurrence(s) of R_6;

R_t and R_z independently represents hydrogen or alkyl;

R_1 is hydrogen, halogen, cyano, hydroxy, amino, alkoxy, alkyl or haloalkyl;

R_2 is hydrogen, halogen, alkyl or haloalkyl;

R_3 is aryl, cycloalkyl, heterocyclyl or a group represented by a formula $-CHR_aR_b$; wherein the aryl, cycloalkyl and heterocyclyl are optionally substituted with 1, 2 or 3 substituent(s) independently selected from halogen, hydroxy, haloalkyl and alkyl;

R_a and R_b independently represent hydrogen, alkyl, alkoxy, alkoxy-alkyl, haloalkyl or cycloalkyl;

R_4 at each occurrence is independently hydrogen, halogen, alkyl, alkoxy, haloalkyl, haloalkoxy or cycloalkyl; or any two adjacent R_4 groups combine together with the atoms to which they are attached to form a fused 5-membered heteroaryl substituted with 1 or 2 occurrence(s) of R_5;

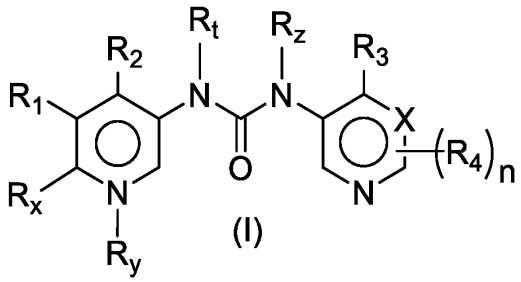
R_5 at each occurrence is independently hydrogen, alkyl, halogen, haloalkyl, cyano, alkoxy, haloalkoxy, amino, aryl, cycloalkyl, heterocycloalkyl or heteroaryl;

R_6 at each occurrence is independently hydrogen, halogen, hydroxy, cyano, alkoxy, alkyl or cycloalkyl; wherein the alkyl is optionally substituted with 1 to 3 substituent(s)

independently selected from hydroxy, oxo, halogen, alkylamino, alkoxy and heterocycloalkyl; and

n is 1, 2 or 3.

In one embodiment, the present invention provides a compound of formula (I):



(I)

or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof; wherein,

X represents N or C;

R_x and R_y combine together with the atoms to which they are attached to form a fused 5-membered heteroaryl substituted with 1 or 2 occurrence(s) of R_6;

R_t and R_z independently represents hydrogen or (C_1-C_6)alkyl;

R_1 is hydrogen, halogen, cyano, hydroxy, amino, (C_1-C_6)alkoxy, (C_1-C_6)alkyl or halo(C_1-C_6)alkyl;

R_2 is hydrogen, halogen, (C_1-C_6)alkyl or halo(C_1-C_6)alkyl;

R_3 is (C_6-C_{10})aryl, (C_3-C_8)cycloalkyl, 5- to 10-membered heterocyclyl or a group represented by a formula -CHR_aR_b; wherein the aryl, cycloalkyl and heterocyclyl are optionally substituted with 1, 2 or 3 substituent(s) independently selected from halogen, hydroxy, halo(C_1-C_6)alkyl and (C_1-C_6)alkyl;

R_a and R_b independently represent hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl or (C_3-C_8)cycloalkyl;

R_4 at each occurrence is independently hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy or (C_3-C_8)cycloalkyl; or any two adjacent R_4 groups combine together with the atoms to which they are attached to form a fused 5-membered heteroaryl substituted with 1 or 2 occurrence(s) of R_5;

R_5 at each occurrence is independently hydrogen, (C_1-C_6)alkyl, halogen, halo(C_1-C_6)alkyl, cyano, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, amino, (C_6-C_{10})aryl, (C_3-C_8)cycloalkyl, 5- to 10-membered heterocycloalkyl or 5- to 10-membered heteroaryl;

R_6 at each occurrence is independently hydrogen, halogen, hydroxy, cyano, (C_1-C_6)alkoxy, (C_1-C_6)alkyl or (C_3-C_8)cycloalkyl; wherein the alkyl is optionally substituted with 1 to 3 substituent(s) independently selected from hydroxy, oxo, halogen, (C_1-C_6)alkylamino, (C_1-C_6)alkoxy and 5- to 10-membered heterocycloalkyl; and

n is 1, 2 or 3.

In one embodiment, X represents N.

In one embodiment, X represents C.

In one embodiment, R_1 represents hydrogen, halogen, cyano, alkoxy or haloalkyl. In one embodiment, R_1 represents hydrogen, halogen, cyano, (C_1-C_6)alkoxy or halo(C_1-C_6)alkyl.

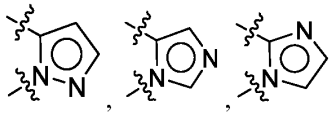
In one embodiment, R_2 represents hydrogen or alkyl. In one embodiment, R_2 represents hydrogen.

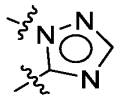
In one embodiment, R_3 is cycloalkyl, heteroaryl, heterocycloalkyl or a group represented by the formula -CHR_aR_b; wherein the cycloalkyl, heteroaryl and heterocycloalkyl are optionally substituted with 1, 2 or 3 substituent(s) independently selected from halogen, haloalkyl and alkyl.

In one embodiment, R_3 is 3- to 10- membered cycloalkyl, 3- to 10-membered heterocycloalkyl or a group represented by the formula -CHR_aR_b; wherein the cycloalkyl and heterocycloalkyl are optionally substituted with 1 or 2 substituent(s) independently selected from halogen, haloalkyl and alkyl.

In one embodiment, R_a and R_b independently represent hydrogen, alkyl, alkoxy, alkoxy-alkyl, haloalkyl or cycloalkyl. In one embodiment, R_a and R_b independently represent hydrogen, alkyl, alkoxy, alkoxy-alkyl or 3- to 10- membered cycloalkyl.

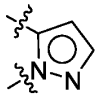
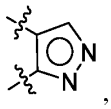
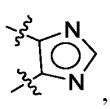
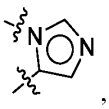
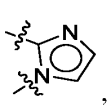
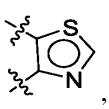
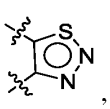
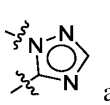
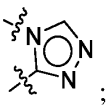
In one embodiment, R_x and R_y combine together with the atoms to which they are attached to form a fused 5-membered heteroaryl substituted with 1 or 2 occurrence(s) of R_6.

In one embodiment, R_x and R_y combine together with the atoms to which they are attached to form a fused 5-membered heteroaryl selected from: 

and  ; wherein ~~~ represents points of fusion; and each ring is substituted with 1 or 2 occurrence(s) of R_6.

In one embodiment, R_4 at each occurrence is independently hydrogen, halogen, alkyl, haloalkyl, haloalkoxy or cycloalkyl. In one embodiment, R_4 at each occurrence is independently hydrogen, halogen or alkyl.

In one embodiment, any two adjacent R_4 groups combine together with the atoms to which they are attached to form a fused 5-membered heteroaryl substituted with 1 or 2 occurrence(s) of R_5.

In one embodiment, any two adjacent R_4 groups combine together with the atoms to which they are attached to form a fused 5-membered heteroaryl selected from:  ,  ,  ,  ,  ,  ,  ,  and  ; wherein ~~~ represents points of fusion; and each ring is substituted with 1 or 2 occurrence(s) of R_5.

In one embodiment, R_5 at each occurrence is independently hydrogen, alkyl, halogen, haloalkyl, haloalkoxy, cyano or cycloalkyl.

In one embodiment, R_5 is hydrogen or halogen.

In one embodiment, R_5 is halogen.

In one embodiment, R_6 at each occurrence is independently hydrogen, halogen, alkyl, alkyl-OH, alkyl-N(alkyl)$_2$, alkoxy-alkyl, haloalkyl, -C(=O)-(5- to 6-membered heterocycloalkyl) or 3- to 10-membered cycloalkyl.

In one embodiment, the present invention provides a compound of formula (I), wherein

X represents N or C;

R_1 represents hydrogen, halogen, cyano, alkoxy or haloalkyl;

R_2 represents hydrogen or alkyl;

R_x and R_y combine together with the atoms to which they are attached to form a fused 5-membered heteroaryl substituted with 1 or 2 occurrence(s) of R_6;

R_3 is 3- to 10-membered cycloalkyl, 3- to 10-membered heterocycloalkyl or a group represented by the formula -CHR_aR_b; wherein the cycloalkyl and heterocycloalkyl are optionally substituted with haloalkyl;

R_a and R_b independently represent hydrogen, alkyl, alkoxy, alkoxy-alkyl or 3- to 10-membered cycloalkyl;

R_4 at each occurrence is independently hydrogen, halogen or alkyl; or any two adjacent R_4 groups combine together with the atoms to which they are attached to form a fused 5-membered heteroaryl substituted with 1 or 2 occurrence(s) of R_5;

R_5 at each occurrence is independently hydrogen, alkyl, halogen haloalkyl, haloalkoxy, cyano or cycloalkyl;

R_6 at each occurrence is independently hydrogen, halogen, alkyl, alkyl-OH, alkyl-$N(alkyl)_2$, alkoxy-alkyl, haloalkyl, -C(=O)-(5- to 6-membered heterocycloalkyl) or 3- to 10-membered cycloalkyl; and

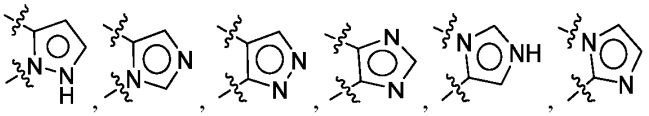
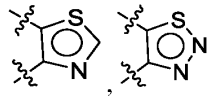
n is 1 or 2.

In one embodiment, the present invention provides a compound of formula (I), wherein

X represents N or C;

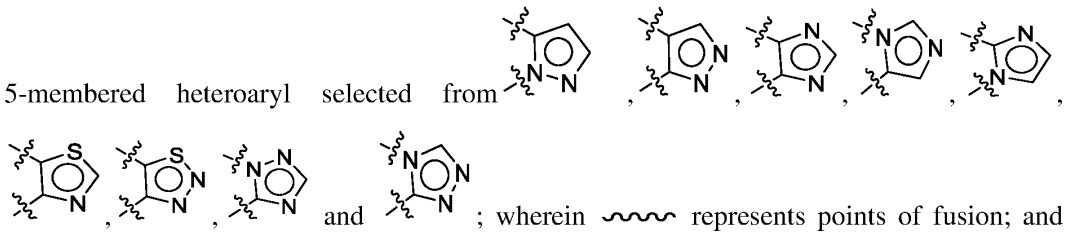
R_1 represents hydrogen, halogen, cyano, alkoxy or halo(C_1-C_6)alkyl;

R_2 represents hydrogen or (C_1-C_6)alkyl;

R_x and R_y combine together with the atoms to which they are attached to form a fused 5-membered heteroaryl selected from  ,  , and  ; wherein ~~~ represents points of fusion; and each ring is substituted with 1 or 2 occurrence(s) of R_6;

R_3 is 3- to 10-membered cycloalkyl, 3- to 10-membered heterocycloalkyl or a group represented by the formula -CHR_aR_b; wherein the cycloalkyl and heterocycloalkyl are optionally substituted with halo(C_1-C_6)alkyl;

R_a and R_b independently represent hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy-(C_1-C_6)alkyl or 3- to 10- membered cycloalkyl;

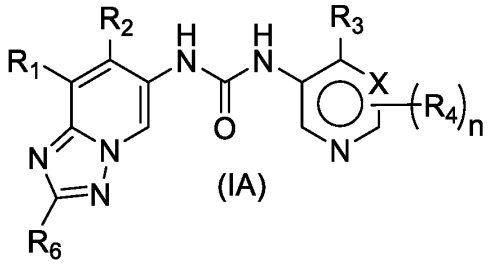
R_4 at each occurrence is independently hydrogen, halogen or (C_1-C_6)alkyl; or any two adjacent R_4 groups combine together with the atoms to which they are attached to form a fused 5-membered heteroaryl selected from  ; wherein ~~~ represents points of fusion; and each ring is optionally substituted with 1 or 2 occurrence(s) of R_5;

R_5 at each occurrence is independently hydrogen, (C_1-C_6)alkyl, halogen, halo(C_1-C_6)alkyl, halo (C_1-C_6)alkoxy, cyano or 3- to 10-membered cycloalkyl;

R_6 at each occurrence is independently hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkyl-OH, (C_1-C_6)alkyl-N(C_1-C_6)alkyl)$_2$, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, -C(=O)-(5- to 6-membered heterocycloalkyl) or 3- to 10- membered cycloalkyl; and

n is 1 or 2.

In one embodiment, the present invention provides compound of formula (IA):



(IA)

or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof; wherein R_1, R_2, R_3, R_4, R_6, X and n are as defined in compound of formula (I).

In one embodiment of formula (IA), X represents N.

In one embodiment of formula (IA), R_1 represents hydrogen, halogen, cyano, (C_1-C_6)alkoxy or halo(C_1-C_6)alkyl.

In one embodiment of formula (IA), R_1 represents hydrogen, halogen, cyano, alkoxy or halo(C_1-C_6)alkyl.

In one embodiment of formula (IA), R_2 represents hydrogen or (C_1-C_6)alkyl.

In one embodiment of formula (IA), R_2 represents hydrogen.

In one embodiment of formula (IA), R_6 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkyl-OH, (C_1-C_6)alkyl-N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkoxy(C_1-C_6)alkyl-, halo(C_1-C_6)alkyl, -C(=O)-(5- to 6-membered heterocycloalkyl) or 3- to 10- membered cycloalkyl.

In one embodiment of formula (IA), R_6 is hydrogen.

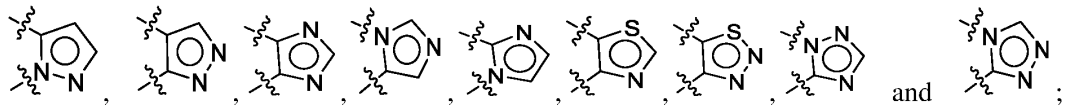
In one embodiment of formula (IA), R_6 is (C_1-C_6)alkyl.

In one embodiment of formula (IA), R_3 is 3- to 10-membered cycloalkyl, 3- to 10-membered heterocycloalkyl or a group represented by the formula -CHR_aR_b; wherein the cycloalkyl and heterocycloalkyl are optionally substituted with halo(C_1-C_6)alkyl;

In one embodiment of formula (IA), R_a and R_b independently represent hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy-(C_1-C_6)alkyl or 3- to 10- membered cycloalkyl.

In one embodiment of formula (IA), R_4 at each occurrence is independently hydrogen, halogen or (C_1-C_6)alkyl; or any two adjacent R_4 groups combine together with the atoms to which they are attached to form a fused 5-membered heteroaryl substituted with 1 or 2 occurrence(s) of R_5.

In one embodiment of formula (IA), any two adjacent R_4 groups combine together with the atoms to which they are attached to form a fused 5-membered heteroaryl selected from



wherein ~~~ represents points of fusion; and each ring is optionally substituted with 1 or 2 occurrence(s) of R_5.

In one embodiment of formula (IA), R_5 represents hydrogen, (C_1-C_6)alkyl, halogen, halo(C_1-C_6)alkyl, halo (C_1-C_6)alkoxy, cyano or 3- to 10-membered cycloalkyl.

In one embodiment, the present invention provides a compound of formula (IA), wherein

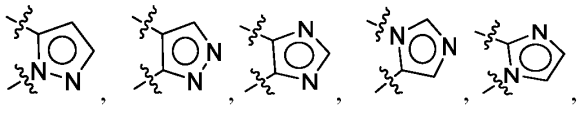
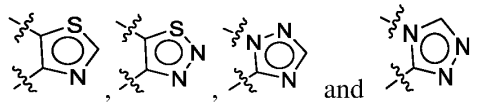
X represents N or C;

R_1 represents hydrogen, halogen, cyano, alkoxy or halo(C_1-C_6)alkyl;

R_2 represents hydrogen or (C_1-C_6)alkyl;

R_3 is 3- to 10-membered cycloalkyl, 3- to 10-membered heterocycloalkyl or a group represented by the formula -CHR_aR_b; wherein the cycloalkyl and heterocycloalkyl are optionally substituted with halo(C_1-C_6)alkyl;

R_a and R_b independently represent hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy-(C_1-C_6)alkyl or 3- to 10- membered cycloalkyl;

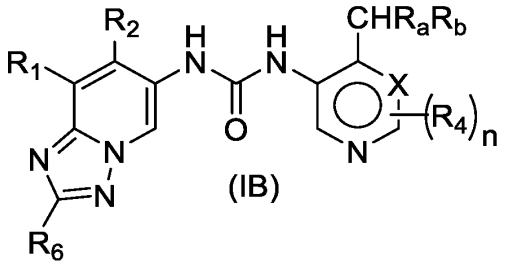
R_4 at each occurrence is independently hydrogen, halogen or (C_1-C_6)alkyl; or any two adjacent R_4 groups combine together with the atoms to which they are attached to form a fused 5-membered heteroaryl selected from  ,  and ; wherein ~~~ represents points of fusion; and each ring is optionally substituted with 1 or 2 occurrence(s) of R_5;

R_5 at each occurrence is independently hydrogen, (C_1-C_6)alkyl, halogen , halo(C_1-C_6)alkyl, halo (C_1-C_6)alkoxy, cyano or 3- to 10-membered cycloalkyl;

R_6 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkyl-OH, (C_1-C_6)alkyl-N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, -C(=O)-(5- to 6-membered heterocycloalkyl) or 3- to 10- membered cycloalkyl; and

n is 1 or 2.

In one embodiment, the present invention provides compound of formula (IB):

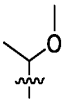


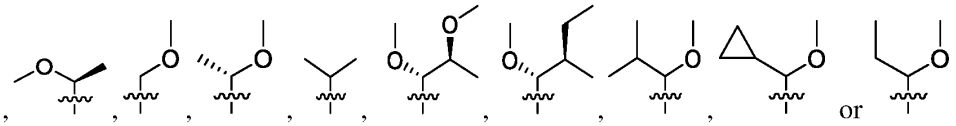
(IB)

or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof; wherein R_1, R_2, R_a, R_b, R_4, R_6, X and n are as defined in compound of formula (I).

In one embodiment of compound of formula (IB), R_1 represents hydrogen, halogen, cyano, (C_1-C_6)alkoxy or halo(C_1-C_6)alkyl.

In one embodiment of compound of formula (IB), R_a and R_b independently represent hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy-(C_1-C_6)alkyl or 3- to 10- membered cycloalkyl.

In one embodiment of compound of formula (IB), the formula -CHR_aR_b represents 

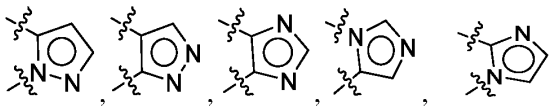
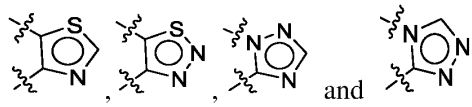
 or ; wherein ~~~ represents point of attachment.

In one embodiment, the present invention provides a compound of formula (IB), wherein

R_1 represents hydrogen, halogen, cyano, (C_1-C_6)alkoxy or halo(C_1-C_6)alkyl;

R_2 represents hydrogen or (C_1-C_6)alkyl;

R_a and R_b independently represent hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy-(C_1-C_6)alkyl or 3- to 10- membered cycloalkyl;

R_4 at each occurrence is independently hydrogen, halogen or (C_1-C_6)alkyl; or any two adjacent R_4 groups combine together with the atoms to which they are attached to form a fused 5-membered heteroaryl selected from  ,  and ; wherein ~~~ represents points of fusion; and each ring is optionally substituted with 1 or 2 occurrence(s) of R_5;

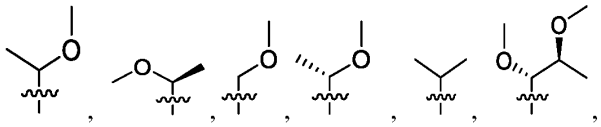
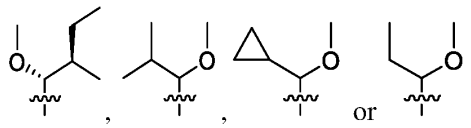
R_5 at each occurrence is independently hydrogen, (C_1-C_6)alkyl, halogen , halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, cyano or 3- to 10-membered cycloalkyl; and

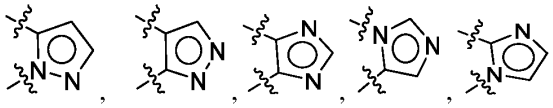
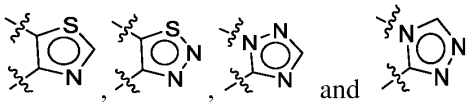
R_6 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkyl-OH, (C_1-C_6)alkyl-N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, -C(=O)-(5- to 6-membered heterocycloalkyl) or 3- to 10- membered cycloalkyl.

In one embodiment, the present invention provides a compound of formula (IB), wherein

R_1 represents hydrogen, halogen, cyano, (C_1-C_6)alkoxy or halo(C_1-C_6)alkyl;

R_2 represents hydrogen or (C_1-C_6)alkyl;

the formula -CHR_aR_b represents  ,  or ; wherein ~~~ represents point of attachment;

R_4 at each occurrence is independently hydrogen, halogen or (C_1-C_6)alkyl; or any two adjacent R_4 groups combine together with the atoms to which they are attached to form a fused 5-membered heteroaryl selected from  ,  and ; wherein ~~~ represents points of fusion; and each ring is optionally substituted with 1 or 2 occurrence(s) of R_5;

R_5 at each occurrence is independently hydrogen, (C_1-C_6)alkyl, halogen , halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, cyano or 3- to 10-membered cycloalkyl; and

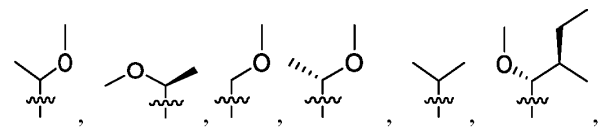
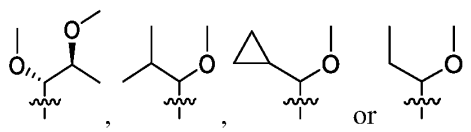
R_6 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkyl-OH, (C_1-C_6)alkyl-N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, -C(=O)-(5- to 6-membered heterocycloalkyl) or 3- to 10- membered cycloalkyl.

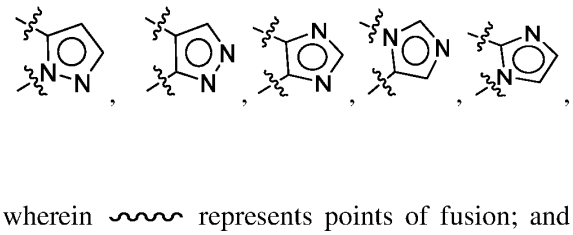
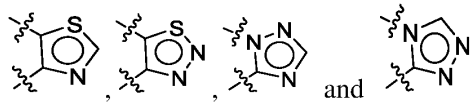
In one embodiment, the present invention provides a compound of formula (IB), wherein

R_1 represents hydrogen, halogen, cyano, (C_1-C_6)alkoxy or halo(C_1-C_6)alkyl;

R_2 represents hydrogen or (C_1-C_6)alkyl;

R_a and R_b independently represent hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy-(C_1-C_6)alkyl or 3- to 10- membered cycloalkyl;

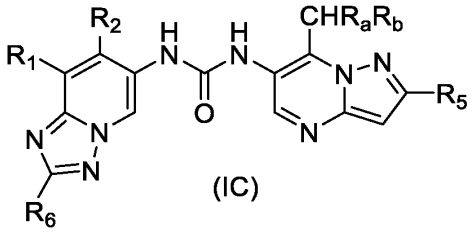
the formula -CHR_aR_b represents  ,  or ; wherein ~~~ represents point of attachment;

R_4 at each occurrence is independently hydrogen, halogen or (C_1-C_6)alkyl; or any two adjacent R_4 groups combine together with the atoms to which they are attached form a fused 5-membered heteroaryl selected from  ,  and ; wherein ~~~ represents points of fusion; and each ring is optionally substituted with 1 or 2 occurrence(s) of R_5;

R_5 at each occurrence is independently hydrogen, (C_1-C_6)alkyl, halogen , halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, cyano or 3- to 10-membered cycloalkyl; and

R_6 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkyl-OH, (C_1-C_6)alkyl-N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, -C(=O)-(5- to 6-membered heterocycloalkyl) or 3- to 10- membered cycloalkyl.

In one embodiment, the present invention provides compound of formula (IC):



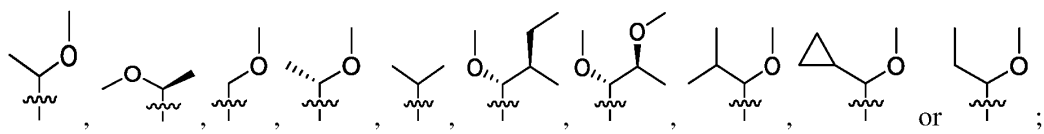
(IC)

or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof; wherein R_1, R_2, R_a, R_b, R_5 and R_6 are as defined in compound of formula (I).

In one embodiment of compound of formula (IC), R_a represents (C_1-C_6)alkoxy.

In one embodiment of compound of formula (IC), R_b represents hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl or 3- to 10- membered cycloalkyl.

In one embodiment of compound of formula (IC), R_b represents (C_1-C_6)alkyl.

In one embodiment of compound of formula (IC), the formula -CHR_aR_b represents  or ; wherein ~~~ represents point of attachment.

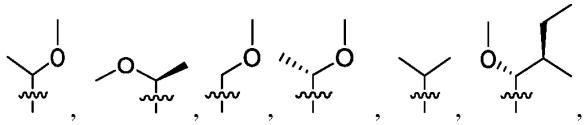
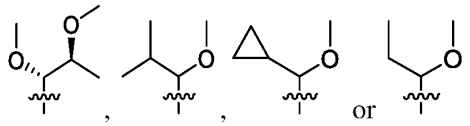
In one embodiment, the present invention provides a compound of formula (IC), wherein

R_1 represents hydrogen, halogen, cyano, (C_1-C_6)alkoxy or halo(C_1-C_6)alkyl;

R_2 represents hydrogen or (C_1-C_6)alkyl;

R_a represents (C_1-C_6)alkoxy;

R_b represents hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl or 3- to 10-membered cycloalkyl;

the formula -CHR_aR_b represents  ,  ; wherein ~~~ represents point of attachment;

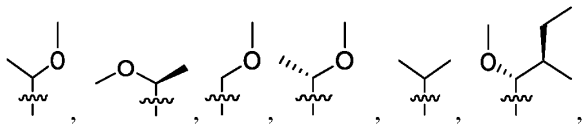
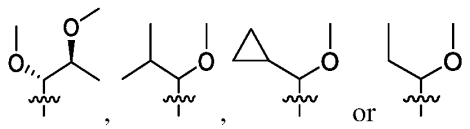
R_5 is hydrogen, (C_1-C_6)alkyl, halogen , halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, cyano or 3- to 10-membered cycloalkyl; and

R_6 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkyl-OH, (C_1-C_6)alkyl-N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, -C(=O)-(5- to 6-membered heterocycloalkyl) or 3- to 10- membered cycloalkyl.

In one embodiment, the present invention provides a compound of formula (IC), wherein

R_1 represents hydrogen, halogen, cyano, (C_1-C_6)alkoxy or halo(C_1-C_6)alkyl;

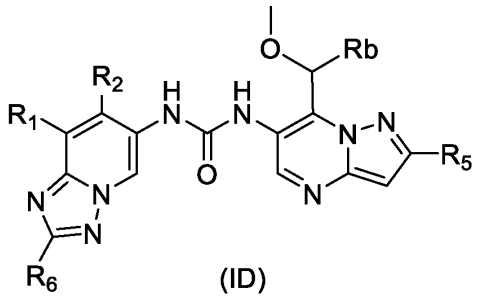
R_2 represents hydrogen or (C_1-C_6)alkyl;

the formula -CHR_aR_b represents  ,  ; wherein ~~~ represents point of attachment;

R_5 is hydrogen, (C_1-C_6)alkyl, halogen , halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, cyano or 3- to 10-membered cycloalkyl; and

R_6 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkyl-OH, (C_1-C_6)alkyl-N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, -C(=O)-(5- to 6-membered heterocycloalkyl) or 3- to 10- membered cycloalkyl.

In one embodiment, the present invention provides compound of formula (ID):



(ID)

or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof; wherein R_1, R_2, R_b, R_5 and R_6 are as defined in compound of formula (I).

In one embodiment of compound of formula (ID), R_b represents hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl or 3- to 10- membered cycloalkyl.

In one embodiment of compound of formula (ID), R_5 is (C_1-C_6)alkyl, halogen, halo(C_1-C_6)alkyl, cyano or 3- to 10-membered cycloalkyl.

In one embodiment, the present invention provides a compound of formula (ID), wherein

R_1 represents hydrogen, halogen, cyano, (C_1-C_6)alkoxy or halo(C_1-C_6)alkyl;

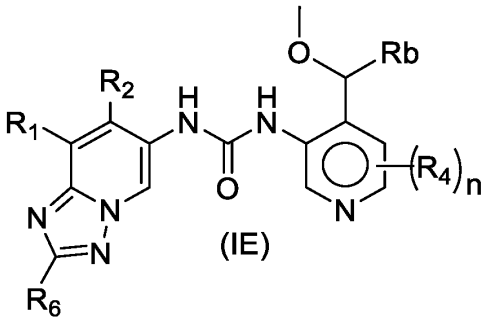
R_2 represents hydrogen or (C_1-C_6)alkyl;

R_b represents hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl or 3- to 10- membered cycloalkyl;

R_5 is (C_1-C_6)alkyl, halogen, halo(C_1-C_6)alkyl, cyano or 3- to 10-membered cycloalkyl; and

R_6 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkyl-OH, (C_1-C_6)alkyl-N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, -C(=O)-(5- to 6-membered heterocycloalkyl) or 3- to 10-membered cycloalkyl.

In one embodiment, the present invention provides compound of formula (IE):



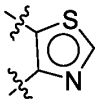
(IE)

or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof; wherein R_1, R_2, R_b, R_4, R_6 and n are as defined in compound of formula (I).

In one embodiment of compound of formula (IE), R_1 represents hydrogen or halogen.

In one embodiment of compound of formula (IE), R_2 represents hydrogen.

In one embodiment of compound of formula (IE), R_b represent $(C_1\text{-}C_6)$alkyl.

In one embodiment of compound of formula (IE), R_4 at each occurrence is independently hydrogen, halogen or $(C_1\text{-}C_6)$alkyl; or any two adjacent R_4 groups combine together with the atoms to which they are attached to form  optionally substituted with 1 or 2 occurrence(s) of halogen, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, cyano or 3- to 10-membered cycloalkyl; wherein ~~~ represents points of fusion.

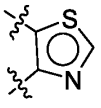
In one embodiment of compound of formula (IE), R_6 is hydrogen or $(C_1\text{-}C_6)$alkyl.

In one embodiment, the present invention provides a compound of formula (IE), wherein

R_1 represents hydrogen or halogen;

R_2 represents hydrogen;

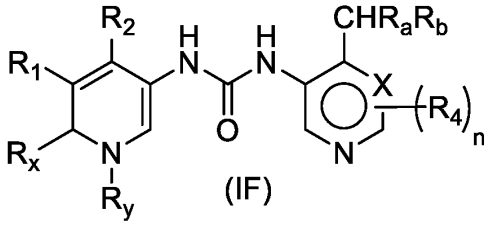
R_b represent $(C_1\text{-}C_6)$alkyl;

R_4 is hydrogen, halogen or $(C_1\text{-}C_6)$alkyl; or any two adjacent R_4 groups combine together with the atoms to which they are attached to form  optionally or substituted with 1 or 2 occurrence(s) of halogen or $(C_1\text{-}C_6)$alkyl; wherein ~~~ represents points of fusion;

R_6 is hydrogen or $(C_1\text{-}C_6)$alkyl; and

n is 1 or 2.

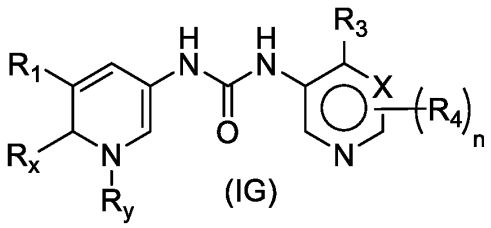
In one embodiment, the present invention provides compound of formula (IF):



(IF)

or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof; wherein R_1, R_2, R_x, Ry, R_a, R_b, R_4, X and n are as defined in compound of formula (I).

In one embodiment, the present invention provides compound of formula (IG):



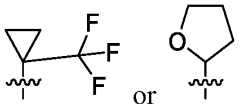
(IG)

or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof; wherein

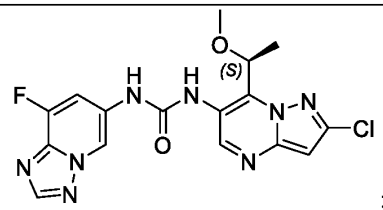
R_3 is 3- to 10-membered cycloalkyl, 3- to 10-membered heterocycloalkyl; and R_1, R_x, Ry, R_4, X and n are as defined in compound of formula (I).

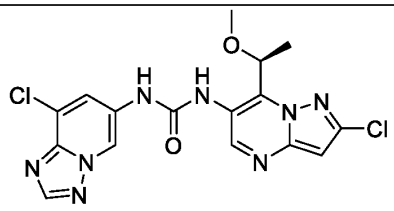
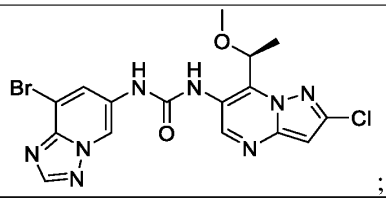
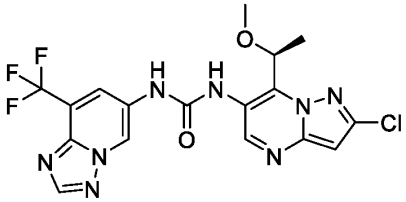
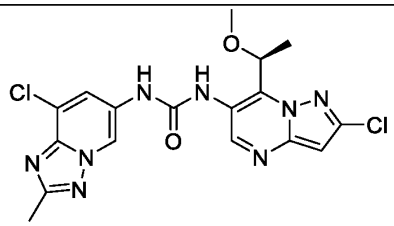
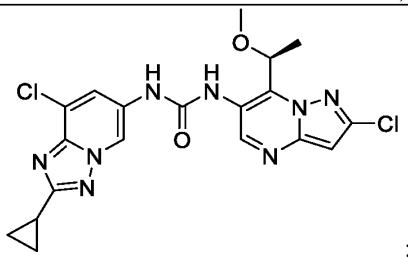
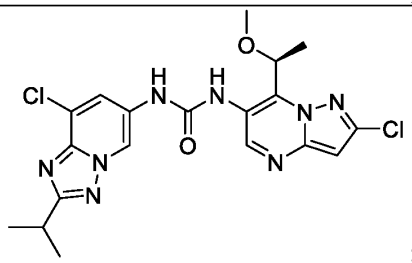
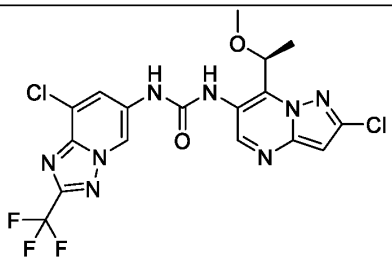
In one embodiment, R_3 is 3- to 8-membered cycloalkyl. In one embodiment, R_3 is  .

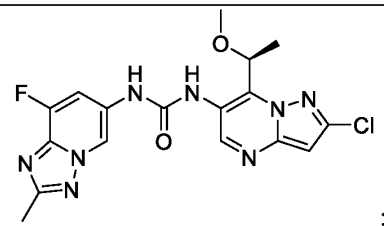
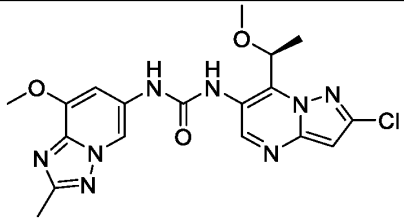
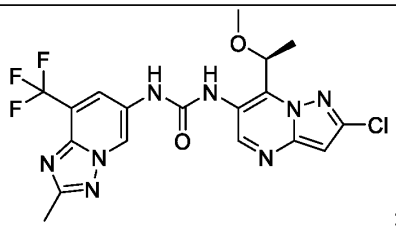
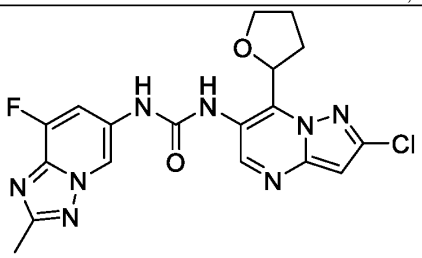
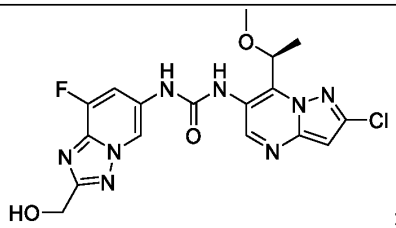
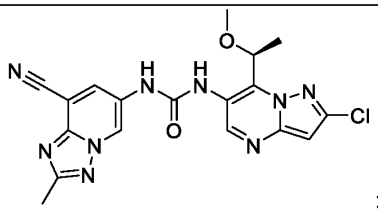
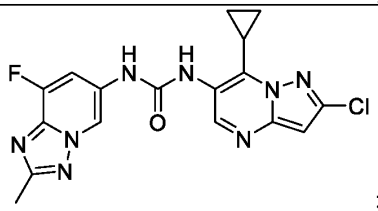
In one embodiment, R_3 is 5- to 6-membered heterocycloalkyl. In one embodiment, R_3 is

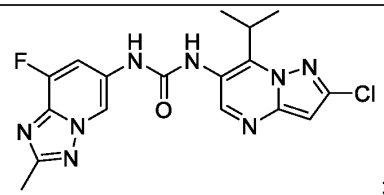
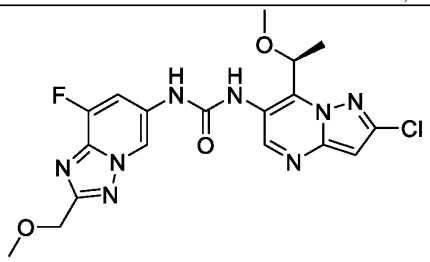
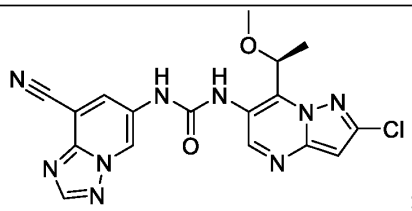
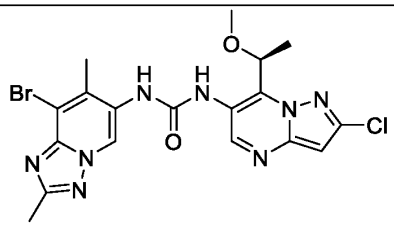
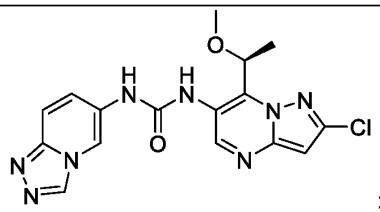
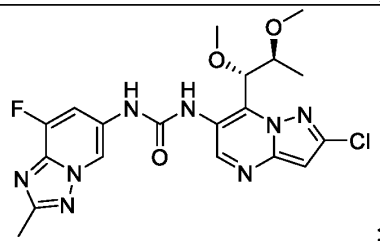
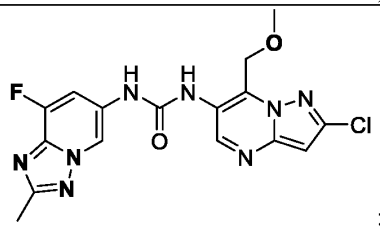
 or .

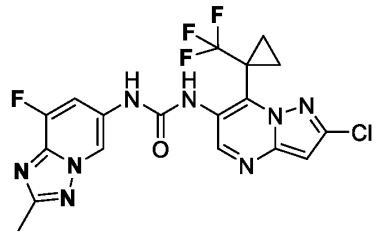
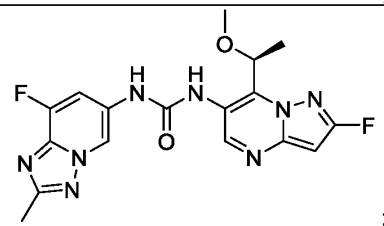
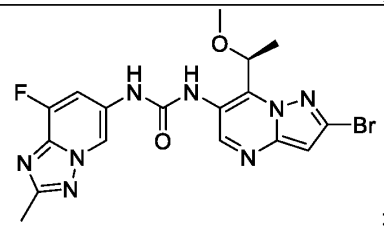
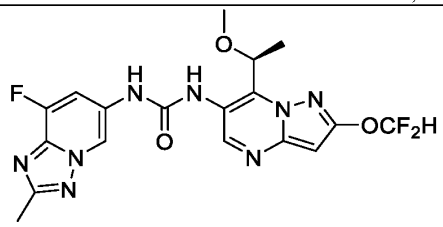
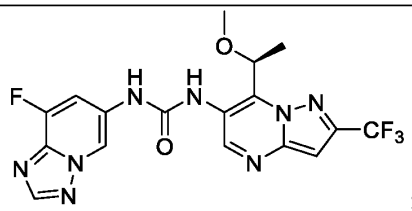
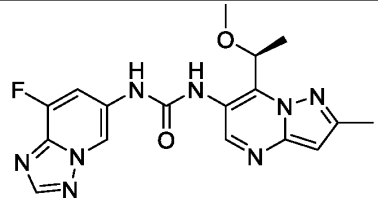
In one embodiment, the present invention provides compound selected from:

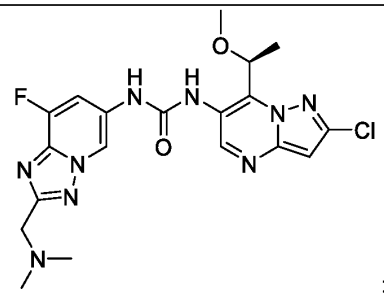
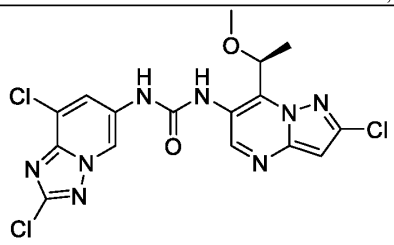
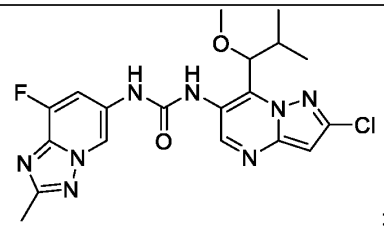
Example	Structure
1	 ;

2	 ;
3	 ;
4	 ;
5	 ;
6	 ;
7	 ;
8	 ;

9	 ;
10	 ;
11	 ;
12	 ;
13	 ;
14	 ;
15	 ;

16	 ;
17	 ;
18	 ;
19	 ;
20	 ;
21	 ;
22	 ;

23	 ;
24	 ;
25	 ;
26	 ;
27	 ;
28	 ;

29	 ;
30	 ;
31	 ;
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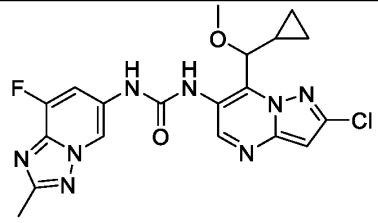
32	 ;
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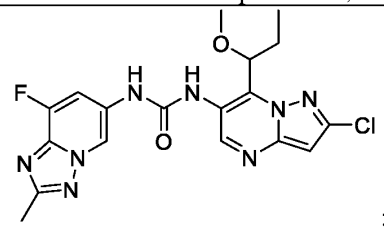
33	 ;
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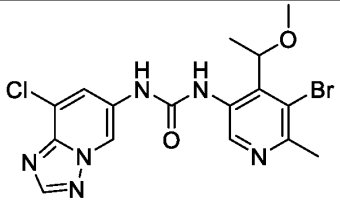
34	 ;

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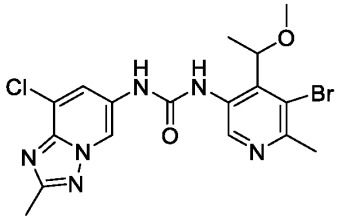
35	 ;
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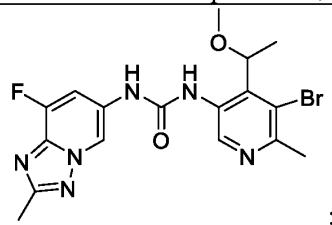
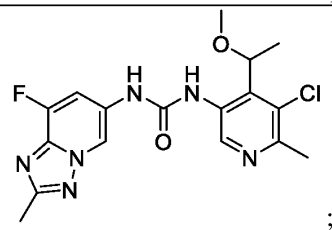
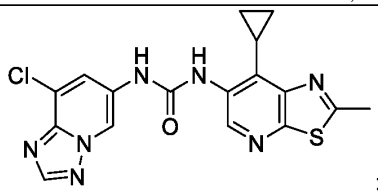
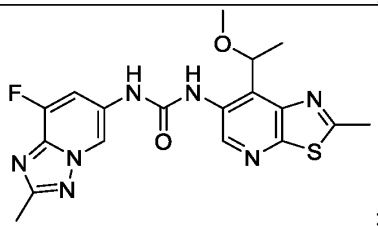
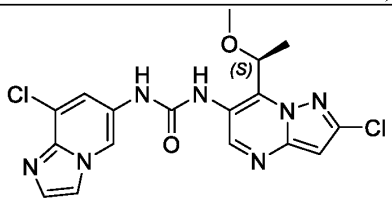
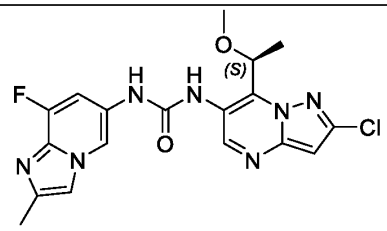
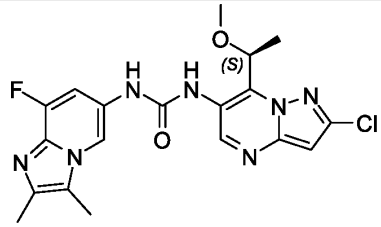
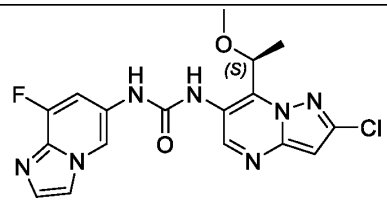
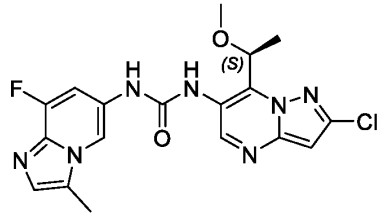
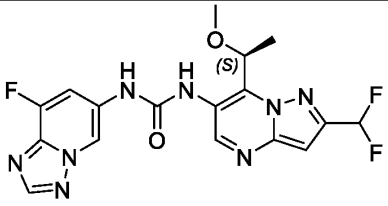
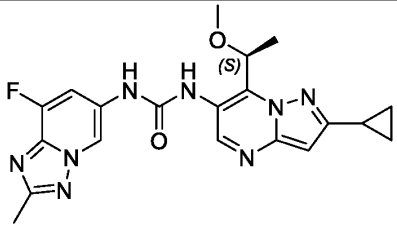
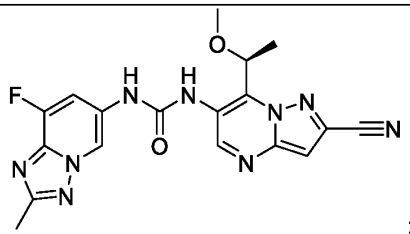
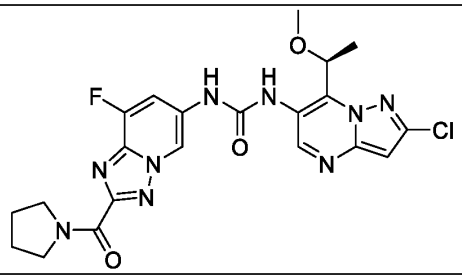
36	 ;
37	 ;
38	 ;
39	 ;
40	 ;

41	 ;
42	 ;
43	 ;
44	 ;
45	 ;
46	 ;
47	 ; and

48	

or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

Method of treatment

In one embodiment, the present invention provides a compound of formula (I) or a pharmaceutical acceptable salt or a stereoisomer or a tautomer thereof, for use as a medicament.

In one embodiment, the present invention provides a compound of formula (I) or a pharmaceutical acceptable salt or a stereoisomer or a tautomer thereof, for use in treating a disease or disorder mediated by MALT-1.

In one embodiment, the present invention provides a pharmaceutical composition comprising compound of formula (I) or a pharmaceutical acceptable salt or a stereoisomer or a tautomer thereof, for use in the manufacture of medicament for the treatment of disease or disorder mediated by MALT-1.

In one embodiment, the present invention provides a method of inhibiting MALT-1 in a subject, comprising administering to the subject, in need thereof, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

In one embodiment, the present invention provides a method of treating a disease or disorder mediated by the inhibition of MALT-1, in a subject comprising administering to the subject in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

In one embodiment, subject is afflicted with a disease or disorder dependent upon MALT-1.

In one embodiment, subject is afflicted with cancer.

In one embodiment, a disease or disorder dependent on MALT-1, includes cancer.

In one embodiment, the cancer is selected from prostate cancer, brain cancer, breast cancer, colorectal cancer, pancreatic cancer, ovarian cancer, lung cancer, cervical cancer, liver cancer, head/neck/throat cancer, skin cancer, bladder cancer or a hematologic cancer. In one embodiment, cancer may comprise a tumour or a blood born cancer. The tumour may be solid.

The tumour is typically malignant and may be metastatic. In one embodiment, the tumour is an adenoma, an adenocarcinoma, a blastoma, a carcinoma, a desmoid tumour, a desmoplastic small round cell tumour, an endocrine tumour, a germ cell tumour, a lymphoma, a leukaemia, a sarcoma, a Wilms tumour, a lung tumour, a colon tumour, a lymph tumour, a breast tumour or a melanoma.

In one embodiment, blastoma comprises hepatoblastoma, glioblastoma, neuroblastoma or retinoblastoma. In one embodiment, carcinoma comprises colorectal carcinoma or hepatocellular carcinoma, pancreatic, prostate, gastric, esophageal, cervical, head and neck carcinomas or adenocarcinoma. In one embodiment, types of sarcoma comprise Ewing sarcoma, osteosarcoma, rhabdomyosarcoma or any other soft tissue sarcoma. In one embodiment, types of melanoma include Lentigo maligna, Lentigo maligna melanoma, Superficial spreading melanoma, Acral lentiginous melanoma, Mucosal melanoma, Nodular melanoma, Polypoid melanoma, Desmoplastic melanoma, Amelanotic melanoma, Soft-tissue melanoma, Melanoma with small nevus-like cells, Melanoma with features of a Spitz nevus and Uveal melanoma. Types of lymphoma and leukaemia include Precursor T-cell leukemia/lymphoma, acute myeloid leukaemia, chronic myeloid leukaemia, acute lymphocytic leukaemia, Follicular lymphoma, Diffuse large B cell lymphoma, Mantle cell lymphoma, chronic lymphocytic leukemia/lymphoma, MALT lymphoma, Burkitt's lymphoma, Mycosis fungoides, Peripheral T-cell lymphoma, Nodular sclerosis form of Hodgkin lymphoma, Mixed-cellularity subtype of Hodgkin lymphoma. Types of lung tumour include tumours of non-small-cell lung cancer (adenocarcinoma, squamous-cell carcinoma and large-cell carcinoma) and small-cell lung carcinoma.

In one embodiment, the disease or disorder mediated by MALT-1 is cancer, selected from bladder cancer, colon cancer, hepatocellular cancer, Small Cell lung cancer or Non-Small Cell lung cancer. In one embodiment of the invention, the cancer is selected from B-cell malignancies such as B-cell lymphoma, e.g. Diffuse large cell B-cell lymphoma (DLBCL) and Mantle cell lymphoma (MCL) and Leukemias, e.g. chronicle lymphatic leukemia (CLL).

In one embodiment, the present invention provides a use of compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, in the manufacture of a medicament for treating or preventing a disease or disorder mediated by MALT-1.

In one embodiment, a disease or disorder dependent on MALT-1, include cancer. In one embodiment, the cancer is selected from bladder cancer, colon cancer, hepatocellular cancer, Small Cell or Non-Small Cell lung cancer. In one embodiment of the invention, the cancer is selected from B-cell malignancies such as B-cell lymphoma, e.g. Diffuse large cell B-cell

lymphoma (DLBCL) and Mantle cell lymphoma (MCL) and Leukemias, e.g. chronicle lymphatic leukemia (CLL).

In certain further embodiment, a disease or disorder dependent on MALT-1, are bladder cancer, colon cancer, hepatocellular cancer, Small Cell lung cancer, Non-Small Cell lung cancer, B-cell lymphoma, e.g. Diffuse large cell B-cell lymphoma (DLBCL), Mantle cell lymphoma (MCL) and Leukemias, e.g. chronicle lymphatic leukemia (CLL).

In certain further embodiment, diseases or disorders mediated by the inhibition of MALT-1, are diffuse large B-cell lymphoma, mantle cell lymphoma, follicular lymphoma, and mucosa-associated lymphoid tissue lymphoma, rheumatoid arthritis, psoriatic arthritis, psoriasis, ulcerative colitis, Crohn's disease, systemic lupus erythematosus, asthma, and chronic obstructive pulmonary disease.

In one embodiment, the present invention provides a use of compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, in the manufacture of a medicament for treating or preventing a disease or disorder mediated by the inhibition of MALT-1.

In one embodiment, the present invention provides a use of pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, in the manufacture of a medicament for treating or preventing cancer, that is mediated by the inhibition of MALT-1.

In one embodiment, cancer is selected from bladder cancer, colon cancer, hepatocellular cancer, Small Cell lung cancer, Non-Small Cell lung cancer, B-cell lymphoma (Diffuse large B-cell lymphoma), mantle cell lymphoma, follicular lymphoma and mucosa-associated lymphoid tissue lymphoma, rheumatoid arthritis, psoriatic arthritis, psoriasis, ulcerative colitis, Crohn's disease, systemic lupus erythematosus, asthma and chronic obstructive pulmonary disease.

Pharmaceutical compositions

In one embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof or a stereoisomer or a tautomer thereof as described herein and at least one pharmaceutically acceptable excipient (such as a pharmaceutically acceptable carrier or diluent). Preferably, the pharmaceutical composition comprises a therapeutically effective amount of at least one compound described herein or a pharmaceutically acceptable salt or a stereoisomer thereof. The compounds described in the present invention may be associated with a pharmaceutically

acceptable excipient (such as a carrier or a diluent) or be diluted by a carrier or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container.

In one embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I), for use in inhibiting MALT-1 in a subject.

In one embodiment, the present invention provides a pharmaceutical composition comprising compound of formula (I) or a pharmaceutical acceptable salt or a stereoisomer or a tautomer thereof, for use as a medicament.

In one embodiment, the present invention provides a pharmaceutical composition comprising compound of formula (I) or a pharmaceutical acceptable salt or a stereoisomer or a tautomer thereof, for use in the manufacture of medicament for the treatment of a disease or disorder dependent upon MALT-1.

In one embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutical acceptable salt or a stereoisomer or a tautomer thereof, for use in treating or preventing of a disease or disorder mediated by MALT-1.

In one embodiment, the disease or disorder mediated by the inhibition of MALT-1 is selected from diffuse large B-cell lymphoma, mantle cell lymphoma, follicular lymphoma and mucosa-associated lymphoid tissue lymphoma, rheumatoid arthritis, psoriatic arthritis, psoriasis, ulcerative colitis, Crohn's disease, systemic lupus erythematosus, asthma and chronic obstructive pulmonary disease.

In one embodiment, the disease or disorder dependent upon MALT-1 is as described herein.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, com, germ, olive, castor and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and

suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this application with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, including but not limited to tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents.

Dosage forms for topical or transdermal administration of a compound of this application include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic

formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this application.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this specification, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this application, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

Administration of the disclosed compounds and pharmaceutical compositions can be accomplished via any mode of administration for therapeutic agents. These modes include systemic or local administration such as oral, nasal, parenteral, intravenous, transdermal, subcutaneous, vaginal, buccal, rectal or topical administration modes.

Depending on the intended mode of administration, the disclosed compounds or pharmaceutical compositions can be in solid, semi-solid or liquid dosage form, such as, for example, injectables, tablets, suppositories, pills, time-release capsules, elixirs, tinctures, emulsions, syrups, powders, liquids, suspensions or the like, sometimes in unit dosages and consistent with conventional pharmaceutical practices. Likewise, they can also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous or intramuscular form and all using forms well known to those skilled in the pharmaceutical arts.

Illustrative pharmaceutical compositions are tablets and gelatin capsules comprising one or more compounds of the present disclosure and a pharmaceutically acceptable carrier, such as, but not limited to, a) a diluent, e.g., purified water, triglyceride oils, such as hydrogenated or partially hydrogenated vegetable oil or mixtures thereof, corn oil, olive oil, sunflower oil, safflower oil, fish oils, such as EPA or DHA or their esters or triglycerides or mixtures thereof, omega-3 fatty acids or derivatives thereof, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, sodium, saccharin, glucose and/or glycine; b) a lubricant, e.g., silica, talcum, stearic acid, its magnesium or calcium salt, sodium oleate, sodium stearate, magnesium stearate,

sodium benzoate, sodium acetate, sodium chloride and/or polyethylene glycol; for tablets also; c) a binder, e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, magnesium carbonate, natural sugars such as glucose or beta- lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, waxes and/or polyvinylpyrrolidone, if desired; d) a disintegrant, e.g., starches, agar, methyl cellulose, bentonite, xanthan gum, alginic acid or its sodium salt or effervescent mixtures; e) absorbent, colorant, flavorant and sweetener; f) an emulsifier or dispersing agent, such as Tween 80, Labrasol, HPMC, DOSS, caproyl 909, labrafac, labrafil, peceol, transcutol, capmul MCM, capmul PG-12, captex 355, gelucire, vitamin E TGPS or other acceptable emulsifier; and/or g) an agent that enhances absorption of the compound such as cyclodextrin, hydroxypropyl-cyclodextrin, PEG400, PEG200.

Liquid, particularly injectable, compositions can, for example, be prepared by dissolution, dispersion, etc. For example, one or more disclosed compound is dissolved in or mixed with a pharmaceutically acceptable solvent such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to thereby form an injectable isotonic solution or suspension. Proteins such as albumin, chylomicron particles or serum proteins can be used to solubilize the disclosed compounds.

One or more disclosed compounds or compositions can be delivered by parental administration. The parental injectable administration is generally used for subcutaneous, intramuscular or intravenous injections and infusions. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions or solid forms suitable for dissolving in liquid prior to injection.

Combination Therapy

The compounds of the present invention may be employed either simultaneously with or before or after, in combination with other anti-cancer agents, e.g. immunomodulating agents, anti-proliferative agents or chemotherapeutic agents or with adjuvants in cancer therapy, e.g. immunosuppressive or anti-inflammatory agents.

The terms “co-administration” or “combined administration” or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single patient and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

In one embodiment, the present invention provides a composition comprising a MALT-1 blocking agent and one or more anti-cancer agent(s): wherein the MALT-1 blocking agent is represented by a compound of formula (I), (IA), (IB), (IC), (ID), (IE), (IF) or (IG) or a compound, salt, stereoisomer, tautomer or composition as described herein.

In one embodiment, anticancer agents that can be combined with the compounds of the present invention may include, but are not limited to, BTK (Bruton's tyrosine kinase) inhibitors such as ibrutinib, SYK inhibitors (such as Fostamatinib, Entospletinib, Cerdulatinib) PKC inhibitors (such as ruboxistaurin, Tamoxifen), PI3K pathway inhibitors (such as Apitolisib, Gedatolisib, Buparlisib, Copanlisib, Duvelisib, Pictilisib, Taselisib), BCL family inhibitors (such as Oblimersen, navitoclax, venetoclax), JAK inhibitors (such as baricitinib, tofacitinib and upadacitinib), PIM kinase inhibitors, rituximab or other B cell antigen-binding antibodies, as well as immune cell redirection agents (e.g. blinatumomab or CAR T-cells) and immunomodulatory agents such as daratumumab, anti-PD-1 antibodies and anti-PD-L1 antibodies.

In one embodiment, provided herein are methods for combination therapy of a compound of formula (I), (IA), (IB), (IC), (ID), (IE), (IF) or (IG) or a compound, salt, stereoisomer, tautomer or composition as disclosed herein with one or more chemotherapeutic agent, therapeutic antibody and/or radiation treatment, e.g., to provide a synergistic or additive therapeutic effect for the treatment of diseases, disorders and conditions such as cancer. In one embodiment, the chemotherapeutic agent is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors and anti-androgens.

For example, further therapeutic agent may comprise an alkylating agent, such as chlorambucil, cyclophosphamide, cisplatin; a mitotic inhibitor such as docetaxel or paclitaxel; an antimetabolite such as 5-fluorouracil, cytarabine, methotrexate or pemetrexed; an anti-tumor antibiotic such as daunorubicin or doxorubicin; a corticosteroid such as prednisone or methylprednisone; a BCL-2 inhibitor such as venetoclax; or immunotherapeutic compound such as nivolumab, pembrolizumab, pidilizumab, avelumab, BMS 936559 or MPDL3280A or a combination thereof. In one embodiment, the immunotherapeutic compound comprises chimeric antigen receptor T cells (CAR T-cells).

In one embodiment, the further therapeutic agent is docetaxel, venetoclax or a hormonal therapy such as fulvestrant. Docetaxel is a type of chemotherapeutic agent known as an

antimicrotubule agent. Docetaxel is used for treating a variety of cancers, such as metastatic prostate cancer. Docetaxel treatment is often administered intravenously and often includes premedication with a corticosteroid such as prednisone. In one embodiment, the further therapeutic agent is venetoclax which is a BCL-2 inhibitor that can induce apoptosis in cancer cells. Venetoclax is typically administered orally.

In some embodiment, compound of formula (I), (IA), (IB), (IC), (ID), (IE), (IF) or (IG) or a compound, salt, stereoisomer, tautomer or composition as disclosed herein can be used in combination with one or more chemotherapeutic agents such as, erlotinib, bortezomib, disulfiram, epigallocatechin gallate, salinosporamide A, carfilzomib, 17-AAG (geldanamycin), radicicol, lactate dehydrogenase A (LDH-A), fulvestrant, sunitinib, letrozole, imatinib mesylate, oxaliplatin, 5-FU (5-fluorouracil),Rapamycin, Lapatinib, lonafarnib, sorafenib, gefitinib, anti-metabolites such as methotrexate; taxoids, e.g., paclitaxel, ABRAXANE® (Cremophor-free), albumin-engineered nanoparticle formulations of paclitaxel (American Pharmaceutical Partners, Schaumberg, Ill.) and docetaxel/doxetaxel; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; platinum analogs such as cisplatin and carboplatin; retinoids such as retinoic acid; and pharmaceutically acceptable salts, acids and derivatives of any of the above.

In some embodiment, compound of formula (I), (IA), (IB), (IC), (ID), (IE), (IF) or (IG) or a compound, salt, stereoisomer, tautomer or composition as disclosed herein can be used in combination with one or more additional pharmaceutical agents such as, chemotherapeutics, anti-inflammatory agents, steroids, immunosuppressants, immune-oncology agents, metabolic enzyme inhibitors, chemokine receptor inhibitors and phosphatase inhibitors, as well as targeted therapies for treatment of diseases, disorders or conditions, such as cancer.

In some embodiment, compound of formula (I), (IA), (IB), (IC), (ID), (IE) (IF) or (IG) or a compound, salt, stereoisomer, tautomer or composition as disclosed herein can be used in combination therapy with one or more kinase inhibitors for the treatment of cancer. Exemplary kinase inhibitors include imatinib, baricitinib, gefitinib, erlotinib, sorafenib, dasatinib, sunitinib, lapatinib, nilotinib, pirfenidone, pazopanib, crizotinib, vemurafenib, vandetanib, ruxolitinib, axitinib, bosutinib, regorafenib, tofacitinib, cabozantinib, ponatinib, trametinib, dabrafenib, afatinib, ibrutinib, ceritinib, idelalisib, nintedanib, palbociclib, lenvatinib, cobimetinib, abemaciclib, acalabrutinib, alectinib, binimetinib, brigatinib, encorafenib, erdafitinib, everolimus, fostamatinib, gilterinib, larotrectinib, lorlatinib, netarsudil, osimertinib, pemigatinib, pexidartinib, ribociclib, temsirolimus, XL-102, XL-092, XL-147, XL-765, XL-499 and XL-880.

In some embodiment, a compound of formula (I), (IA), (IB), (IC), (ID), (IE), (IF) or (IG) or a compound, salt, stereoisomer, tautomer or composition as disclosed herein can be used in combination with a HSP90 inhibitor (e.g., XL888), liver X receptor (LXR) modulators, retinoid-related orphan receptor gamma (RORγ) modulators, checkpoint inhibitors such as a CK1 inhibitor or a CK1α inhibitor, a Wnt pathway inhibitor (e.g., SST-215) or a mineralocorticoid receptor inhibitor, (e.g., esaxerenone), or Poly ADP ribose polymerase (PARP) inhibitors, such as, olaparib, rucaparib, niraparib, talazoparib for the treatment of cancer.

In some embodiment, for the treatment of cancer, a compound of formula (I), (IA), (IB), (IC), (ID), (IE), (IF) or (IG) or a compound, salt, stereoisomer, tautomer or composition as disclosed herein can be used in combination with one or more immune check point inhibitors, for example, inhibitors of PD-l or inhibitors of PD-L1, e.g., an anti-PD-l monoclonal antibody or an anti-PD-L1 monoclonal antibody, for example, nivolumab (Opdivo), pembrolizumab (Keytruda, MK-3475), atezolizumab, avelumab, cemiplimab, spartalizumab, camrelizumab, cetrelimab, toripalimab, sintilimab, AB122, JTX-4014, BGB-108, BCD-100, BAT1306, LZM009, AK105, HLX10 and TSR-042, AMP-224, AMP- 514, PDR001, durvalumab, pidilizumab (Imfinzi®, CT-011), CK-301, BMS 936559 and MPDL3280A. In some embodiment, the anti-PD-1 monoclonal antibody is nivolumab, pembrolizumab, pidilizumab, PDR001, MGA012, PDR001, AB122 or AMP-224. In some embodiment, the anti-PD-1 monoclonal antibody is nivolumab or pembrolizumab. In some embodiment, the anti-PD1 antibody is pembrolizumab. In some embodiment, the anti-PD1 antibody is nivolumab.

In some embodiment, for the treatment of cancer, compound of formula (I), (IA), (IB), (IC), (ID), (IE), (IF) or (IG) or a compound, salt, stereoisomer, tautomer or composition as disclosed herein can be used in combination with one or more inhibitors of PD-L1. Antibodies that bind to human PD-L1 include atezolizumab, avelumab, durvalumab, tislelizumab, BMS-935559, MEDI4736, FAZ053, KN035, CS1001, CBT-502, A167, STI-A101, CK-301, BGB-A333, MSB-2311, HLX20, KN035, and LY3300054. In some embodiment, the anti-PD-Ll monoclonal antibody is BMS-935559, MEDI4736, MPDL3280A or MSB0010718C. In some embodiment, the anti-PD-Ll monoclonal antibody is atezolizumab, avelumab, durvalumab.

In some embodiment, for treatment of cancer, a compound of formula (I), (IA), (IB), (IC), (ID), (IE), (IF) or (IG) or a compound, salt, stereoisomer, tautomer or composition as disclosed herein can be used in combination with one or more CTLA-4 inhibitors, e.g., an anti-CTLA-4 antibody, for example, ipilimumab (Yervoy), tremelimumab and AGEN1884; and phosphatidylserine inhibitors, for example, bavituximab (PGN401); antibodies to cytokines

(IL-10, TGF-b and the like); other anti-cancer agents such as cemiplimab. In some embodiment, the inhibitor of an immune checkpoint molecule is an inhibitor of PD-L1 and CTLA-4, e.g., an anti-PD-L1/CTLA-4 bispecific antibody or an anti-PD-1/CTLA-4 bispecific antibody. Bispecific antibodies that bind to PD-L1 and CTLA-4 include AK104.

In one embodiment, the present invention provides a composition comprising a compound of formula (I), (IA), (IB), (IC), (ID), (IE), (IF) or (IG) or a compound, salt, stereoisomer, tautomer or composition as disclosed herein in combination with one or more other therapeutic agents and a pharmaceutically acceptable excipient or carrier. The compound of formula (I), (IA), (IB), (IC), (ID), (IE), (IF) or (IG) or a compound, salt, stereoisomer, tautomer or composition as disclosed herein may be administered in combination with one or more other therapeutic agents (preferably one or two, more preferably one): (1) to complement and/or enhance prevention and/or therapeutic efficacy of the preventive and/or therapeutic drug effect of the compound of the present invention, (2) to modulate pharmacodynamics, improve absorption improvement or reduce dosage reduction of the preventive and/or therapeutic compound of the present invention and/or (3) to reduce or ameliorate the side effects of the preventive and/or therapeutic compound of the present invention. As used herein, the phrase "conjoint administration" refers to any form of administration of two or more different therapeutic compounds such that the second compound is administered while the previously administered therapeutic compound is still effective in the body (e.g., the two compounds are simultaneously effective in the patient, which may include synergistic effects of the two compounds).

For example, the different therapeutic compounds can be administered either in the same formulation or in a separate formulation, concomitantly, sequentially or separately. In one embodiment, the different therapeutic compounds can be administered within one hour, 12 hours, 24 hours, 36 hours, 48 hours, 72 hours or a week of one another. Thus, an individual who receives such treatment can benefit from a combined effect of different therapeutic compounds. The respective compounds may be administered by the same or different route and the same or different method. In one embodiment, the other therapeutic compounds can be administered within one hour, 12 hours, 24 hours, 36 hours, 48 hours, 72 hours or a week prior to or after administration of a compound of formula (I), (IA), (IB), (IC), (ID), (IE), (IF) or (IG) or a compound, salt, stereoisomer, tautomer or composition as disclosed herein. In one embodiment, the other therapeutic compounds can be administered within 0.5 hours to 24 hours prior to or after administration of a compound of formula (I), (IA), (IB), (IC), (ID), (IE), (IF) or (IG) or a compound, salt, stereoisomer, tautomer or composition as disclosed herein. In one

embodiment, the other therapeutic compounds can be administered within 0.5 hours to 72 hours prior to or after administration of a compound of formula (I), (IA), (IB), (IC), (ID), (IE), (IF) or (IG) or a compound, salt, stereoisomer, tautomer or composition as disclosed herein. In one embodiment, the other therapeutic compounds can be administered within 2 hours prior to or after administration of a compound of formula (I), (IA), (IB), (IC), (ID), (IE), (IF) or (IG) or a compound, salt stereoisomer, tautomer or composition as disclosed herein.

A concomitant medicine comprising the compound of the present invention and other drug may be administered as a combination preparation in which both components are contained in a single formulation or administered as separate formulations. The administration by separate formulations includes simultaneous administration or administration of the formulations separated by some time intervals. In the case of the administration with some time intervals, the compound of the present invention can be administered first, followed by another drug or another drug can be administered first, followed by the compound of the present invention, so long as the two compounds are simultaneously active in the patient at least some of the time during the conjoint therapy. The administration method of the respective drugs may be administered by the same or different route and the same or different method.

The dosage of the other drug can be properly selected, based on a dosage that has been clinically used or may be a reduced dosage that is effective when administered in combination with a compound of the present invention. The compounding ratio of the compound of the present invention and the other drug can be properly selected according to age and weight of a subject to be administered, administration method, administration time, disorder to be treated, symptom and combination thereof. For example, the other drug may be used in an amount of about 0.01 to about 100 parts by mass, based on 1 part by mass of the compound of the present invention. The other drug may be a combination of two or more kind of arbitrary drugs in a proper proportion. The other drug that complements and/or enhances the preventive and/or therapeutic efficacy of the compound of the present invention includes not only those that have already been discovered, but those that will be discovered in future, based on the above mechanism.

In one embodiment, the present compound of formula (I), (IA), (IB), (IC), (ID), (IE), (IF) or (IG) or a compound, salt, stereoisomer, tautomer or composition as disclosed herein thereof may be conjointly administered with non-chemical methods of cancer treatment. In one embodiment, the compound of formula (I), (IA), (IB), (IC), (ID), (IE), (IF) or (IG) or a compound, salt, stereoisomer, tautomer or composition as disclosed herein can be conjointly administered with non-chemical methods of cancer treatment. In one embodiment, the

compound of formula (I), (IA), (IB), (IC), (ID), (IE), (IF) or (IG) or a compound, salt, stereoisomer, tautomer or composition as disclosed herein can be conjointly administered with radiation therapy. In one embodiment, the compound of formula (I), (IA), (IB), (IC), (ID), (IE), (IF) or (IG) or a compound, salt, stereoisomer, tautomer or composition as disclosed herein can be conjointly administered with surgery, with thermoablation, with focused ultrasound therapy, with cryotherapy or with any combination of these.

DEFINITIONS

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in art to which the subject matter herein belongs. As used in the specification and the appended claims, unless specified to the contrary, the following terms have the meaning indicated in order to facilitate the understanding of the present invention.

The singular forms "a", "an" and "the" encompass plural references unless the context clearly indicates otherwise.

As used herein, the terms "optional" or "optionally" mean that the subsequently described event or circumstance may occur or may not occur and that the description includes instances where the event or circumstance occurs as well as instances in which it does not. In other words, "optionally substituted" refers to an event or circumstance in which the substituent is present as well as the event or circumstance in which the substituent is absent. For example, "optionally substituted alkyl" refers to an event or circumstance in which the said alkyl may be substituted as well as the event or circumstance in which the alkyl is not substituted. The term "optionally substituted alkyl" can also be referred to as 'unsubstituted or substituted alkyl' group, wherein the substituent(s) are as stated therein.

The term "substituted" refers to moieties having substituent(s) replacing hydrogen on one or more carbons of the backbone. It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term "substituted" is contemplated to include all permissible substituent(s) of organic compounds. In a broad aspect, the permissible substituent(s) include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituent(s) of organic compounds. The permissible substituent(s) can be one or more and the same or different for appropriate organic

compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituent(s) and/or any permissible substituent(s) of organic compounds described herein which satisfy the valences of the heteroatoms. Unless specifically stated, the substituent(s) can include any substituent(s) described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl or an acyl), a thiocarbonyl (such as a thioester, a thioacetate or a thioformate), an alkoxyl, an oxo, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heteroaryl, a heterocycloalkyl, an aralkyl or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that substituent(s) can themselves be substituted, if appropriate.

As used herein, the term "alkyl" refers to saturated aliphatic groups, including but not limited to C_1-C_{10} straight-chain alkyl groups or C_3-C_{10} branched-chain alkyl groups. Preferably, the "alkyl" group refers to C_1-C_6 straight-chain alkyl groups or C_3-C_6 branched-chain alkyl groups. In one embodiment, the "alkyl" group refers to C_1-C_6 alkyl groups. In another embodiment, the "alkyl" group refers to C_1-C_4 alkyl groups. Examples of "alkyl" include, but are not limited to, methyl, ethyl, 1-propyl, 2-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, 1-pentyl, 2-pentyl, 3-pentyl, neo-pentyl, 1-hexyl, 2-hexyl, 3-hexyl, 1-heptyl, 2-heptyl, 3-heptyl, 4-heptyl, 1-octyl, 2-octyl, 3-octyl and 4-octyl. The "alkyl" group may be optionally substituted. In one embodiment, the term "optionally substituted alkyl" can also be referred to as 'unsubstituted or substituted alkyl' group, wherein the substituent(s) are as stated therein.

As used herein, the term "alkylamino" refers to an amino group substituted with one or two alkyl group(s), wherein the alkyl group is as defined above. In one embodiment, "alkylamino" refers to (C_1-C_6)alkylamino groups. Examples of "alkylamino" include but are not limited to -NH(CH_3), -N(CH_3)$_2$, -NH(C_2H_5) and -NH(C_2H_5)$_2$.

As used herein, the term "halo" or "halogen" alone or in combination with other term(s) means fluorine, chlorine, bromine or iodine.

As used herein, the term "haloalkyl" refers to alkyl substituted with one or more halogen atoms, wherein the halo and alkyl groups are as defined above. In one embodiment, haloalkyl contains halo(C_1-C_6)alkyl and preferably halo(C_1-C_4)alkyl. Examples of "haloalkyl" include but are not limited to fluoromethyl, difluoromethyl, chloromethyl, trifluoromethyl and 2,2,2-trifluoroethyl.

As used herein the term “cycloalkyl” alone or in combination with other term(s) means C3-C10 saturated cyclic hydrocarbon ring. A cycloalkyl may be a single ring, or polycyclic ring which typically contains from 3 to 8 carbon ring atoms. Examples of single-ring cycloalkyls include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. A cycloalkyl may alternatively be polycyclic or contain more than one ring. Examples of polycyclic cycloalkyls include bridged, fused and spirocyclic carbocyclyls and the like. In one embodiment, cycloalkyl refers to (C_3–C_{10})cycloalkyl. The cycloalkyls group can be unsubstituted or substituted with one or more substituents wherein the substitutent is described herein. In one embodiment, the term “optionally substituted cycloalkyl” can also be referred to as ‘unsubstituted or substituted cycloalkyl’ group, wherein the substituent(s) are as stated therein.

As used herein, the term “aryl” is optionally substituted monocyclic, bicyclic or polycyclic aromatic hydrocarbon ring system of about 6 to 14 carbon atoms. In one embodiment, “aryl” refers to C_6-C_{10} aryl group. Examples of a C_6-C_{14} aryl group include, but are not limited to, phenyl, naphthyl, biphenyl, anthryl, fluorenyl, indanyl, biphenylenyl and acenaphthyl. Aryl group can be unsubstituted or substituted with one or more suitable groups. The term “optionally substituted aryl” can also be referred to as ‘unsubstituted or substituted aryl’ group, wherein the substituent(s) are as stated therein.

As used herein, the term “heterocyclyl” or "heterocyclic" alone or in combination with other term(s) includes both "heterocycloalkyl" and "heteroaryl" groups which are as described herein.

As used herein, the term “heterocycloalkyl” refers to a non-aromatic, saturated or partially saturated, bridged bicyclic, spirocyclic, monocyclic or polycyclic ring system of 3 to 15 member, unless the ring size is specifically mentioned, having at least one heteroatom or hetero group selected from O, N, S, S(O), $S(O)_2$ and NH with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen and sulfur. The term “heterocycloalkyl” also refers to the bridged bicyclic ring system having at least one heteroatom or hetero group selected from O, N, S, S(O), $S(O)_2$ and NHExamples of “heterocycloalkyl” include, but not limited to, azetidinyl, oxetanyl, imidazolidinyl, pyrrolidinyl, oxazolidinyl, thiazolidinyl, pyrazolidinyl, tetrahydrofuranyl, piperidinyl, dihydropyridinyl, piperazinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, 1,4-dioxanyl, dioxidothiomorpholinyl, oxapiperazinyl, oxapiperidinyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiophenyl, dihydropyranyl, indolinyl, indolinylmethyl, isoindolinyl, oxoisoindolinyl, dioxoisoindolinyl, aza-bicyclooctanyl, diazabicyclooctanyl, azocinyl,

chromanyl, isochromanyl, xanthenyl and 2-oxa-6-azaspiro[3.3]heptanyl. Attachment of a heterocycloalkyl substituent can occur via either a carbon atom or a heteroatom. A heterocycloalkyl group can be optionally substituted with one or more suitable groups by one or more aforesaid groups. Preferably, heterocycloalkyl" refers to 5- to 10-membered ring (unless the ring size is specifically mentioned). More preferably, "heterocycloalkyl" refers to 5- to 6-membered ring (unless the ring size is specifically mentioned). Examples of a heterocycloalkyl group include, but are not limited to, imidazolidinyl, pyrrolidinyl, oxazolidinyl, thiazolidinyl, pyrazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl and thiomorpholinyl. All heterocycloalkyl are optionally substituted by one or more aforesaid groups. In one embodiment, the term "optionally substituted heterocycloalkyl" can also be referred to as 'unsubstituted or substituted heterocycloalkyl' group, wherein the substituent(s) are as stated therein.

As used herein, the term "heteroaryl" refers to a completely unsaturated ring system containing a total of 5 to 20 ring atoms, unless the ring size is specifically mentioned. At least one of the ring atoms is a heteroatom (i.e., O, N or S), with the remaining ring atoms/groups being independently selected from C, N, O and S. A heteroaryl may be a single-ring (monocyclic) or multiple rings (bicyclic, tricyclic or polycyclic) fused together or linked covalently. Preferably, "heteroaryl" is a 5- to 10-membered ring, unless the ring size is specifically mentioned. More preferably, "heteroaryl" is a 5- to 6-membered ring, unless the ring size is specifically mentioned. The rings may contain from 1 to 4 additional heteroatoms selected from N, O and S, wherein the N atom is optionally quarternized. Any suitable ring position of the heteroaryl moiety may be covalently linked to the defined chemical structure. Examples of "heteroaryl" include but not limited to furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, cinnolinyl, isoxazolyl, thiazolyl, isothiazolyl, 1H-tetrazolyl, oxadiazolyl, triazolyl, pyridyl (pyridinyl), 3-fluoropyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzofuranyl, benzothienyl, benzotriazinyl, phthalazinyl, thianthrene, dibenzofuranyl, dibenzothienyl, benzimidazolyl, indolyl, isoindolyl, indazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, purinyl, pteridinyl, 9H-carbazolyl, α-carbolinyl, indolizinyl, benzoisothiazolyl, benzoxazolyl, pyrrolopyridyl, purinyl, benzothiadiazolyl, benzooxadiazolyl, benzotriazolyl, benzotriadiazolyl, carbazolyl, dibenzothienyl, acridinyl and the like. Heteroaryl group may be optionally further substituted. In one embodiment, the term "optionally substituted heteroaryl" can also be referred to as 'unsubstituted or substituted heteroaryl' group, wherein the substituent(s) are as stated therein.

In one embodiment, heteroaryl (e.g., pyridine or pyridyl) can be optionally substituted by oxo to form a respective pyridine-N-oxide or pyridyl-N-oxide.

As used herein, the term "amino" refers to an $-NH_2$ group.

As used herein, the term "hydroxy" alone or in combination with other term(s) means –OH.

As used herein, the term "oxo" refers to =O group.

As used herein, the term "alkoxy" refers to the group -O-alkyl, where the alkyl groups are as defined above. Exemplary C_1-C_{10} alkoxy group include but are not limited to methoxy, ethoxy, n-propoxy, n-butoxy or t-butoxy. In one embodiment, the "alkoxy" group refers to C_1-C_6 alkoxy groups. In another embodiment, the "alkoxy" group refers to C_1-C_4 alkoxy groups. An alkoxy group can be optionally substituted with one or more suitable groups. In some emodiments, alkoxy group can be unsubstituted or substituted with one or more substitutents, wherein the substitutetns are described herein.

As used herein, the term "alkoxy-alkyl" refers to an alkyl group substituted with one or more alkoxy groups, wherein the alkyl and alkoxy groups are as defined above. In one embodiment, alkoxy-alkyl represents (C_1-C_6)alkoxy-(C_1-C_6)alkyl and preferably (C_1-C_4)alkoxy-(C_1-C_4)alkyl. Exemplary alkoxy-alkyl group include, but are not limited to methoxymethyl, ethoxymethyl and ethoxyethyl. In one embodiment, the point of attachment of 'alkoxy-alkyl' group to the rest of the moiety is via alkyl group.

As used herein, the term "haloalkoxy" refers to an alkoxy group substituted with one or more halogen atoms (i.e., haloC_{1-8}alkoxy). In one embodiment, 'haloalkoxy' refers to halo(C_1-C_6)alkoxy. Examples of "haloalkoxy" include, but are not limited, to fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, pentafluoroethoxy, pentachloroethoxy, chloromethoxy, dichlorormethoxy, trichloromethoxy and 1-bromoethoxy.

The term "heteroatom" as used herein refers to a sulfur, nitrogen or oxygen atom.

As used herein, the term "comprises" or "comprising" is generally used in the sense of include, that is to say permitting the presence of one or more features or components.

As used herein, the term 'compound(s)' comprises the compound(s) disclosed in the present invention.

As used herein, the term "including" as well as other forms, such as "include", "includes" and "included" is not limiting.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By

"pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

As used herein, the term "pharmaceutical composition" refers to a composition(s) containing a therapeutically effective amount of at least one compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof; and a pharmaceutically acceptable carrier, as described herein.

The term "tautomer" refers to compounds in which hydrogen atoms are transposed to other parts of the molecules and the chemical bonds between the atoms of the molecules are consequently rearranged. Compounds of the present invention, free form and salts thereof, may exist in multiple tautomeric forms. It is understood that all tautomeric forms, insofar as they may exist, are included within the invention. For example, pyridine or pyridyl can be optionally substituted by oxo to form a respective pyridone or pyridon-yl and may include its tautomeric form such as a respective hydroxy-pyridine or hydroxy-pyridyl, provided said tautomeric form may be obtainable.

The pharmaceutical composition(s) usually contain(s) about 1% to 99%, for example, about 5% to 75% or from about 10% to about 30% by weight of the compound of formula (I) or (II) or pharmaceutically acceptable salts thereof. The amount of the compound of formula (I) or pharmaceutically acceptable salts thereof in the pharmaceutical composition(s) can range from about 1 mg to about 1000 mg or from about 2.5 mg to about 500 mg or from about 5 mg to about 250 mg or in any range falling within the broader range of 1 mg to 1000 mg or higher or lower than the aforementioned range.

As used herein, "pharmaceutically acceptable carrier, diluent or excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, surfactant or emulsifier that has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

The term "administer," "administering," or "administration" as used in this disclosure refers to either directly administering one or more disclosed compounds or a pharmaceutically acceptable salt of one or more disclosed compounds or a composition comprising one or more disclosed compounds to a subject or analog of the compound or a pharmaceutically acceptable salt of the compound or composition to the subject, which can form an equivalent amount of active compound within the subject's body.

The term "carrier" as used in this disclosure, encompasses carriers, excipients and diluents and means a material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting a pharmaceutical agent from one organ or portion of the body, to another organ or portion of the body of a subject.

As used herein, the term "treat", "treating" and "treatment" refer to a method of alleviating or abrogating a disease and/or its attendant symptoms.

As used herein, the term "prevent", "preventing" and "prevention" refer to a method of preventing the onset of a disease and/or its attendant symptoms or barring a subject from acquiring a disease.

As used herein, the term "subject" refers to an animal, preferably a mammal and most preferably a human.

As used herein, the term, "therapeutically effective amount" refers to an amount of a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer thereof or a tautomer; or a composition comprising the compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, effective in producing the desired therapeutic response in a particular subject suffering from a diseases or disorder mediated by MALT-1, in particular their use in diseases or disorder associated with cancer. Particularly, the term "therapeutically effective amount" includes the amount of the compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, when administered, that elicits a positive modification or alteration in the disease or disorder to be treated or is sufficient to effectively prevent development of or alleviate to some extent, one or more of the symptoms associated with the disease or disorder being treated in a subject. In respect of the therapeutic amount of the compound, the amount of the compound used for the treatment of a subject is low enough to avoid undue or severe side effects, within the scope of sound medical judgment can also be considered. The therapeutically effective amount of the compound or composition will be varied depending upon factors such as the condition of the subject being treated, the severity of the condition being treated or prevented, the duration of the treatment, the nature of concurrent therapy, the age and physical condition of the end user, the specific compound or composition employed the particular pharmaceutically acceptable carrier utilized.

"Pharmaceutically acceptable" means that, which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary as well as human pharmaceutical use.

The term "pharmaceutically acceptable salt" refers to a product obtained by reaction of the compound of the present invention with a suitable acid or a base. In some cases, a medicament can be present in the form of a pharmaceutically acceptable salt. In some instances, a pharmaceutically acceptable salt can be a salt described in Berge et al, J. Pharm. Sci, 1977. In some instances, a pharmaceutically acceptable salts can include those salts derived from a mineral organic acid or inorganic base. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present invention include the non- toxic salts of the parent compound formed, e.g., from non-toxic inorganic or organic acids.

The pharmaceutically acceptable salts of the present invention can be prepared from a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of the compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg or K hydroxide, carbonate, bicarbonate or the like) or by reacting free base forms of the compounds with a stoichiometric amount of the appropriate acid (such as organic or inorganic acids). Such reactions are typically carried out in water or in an organic solvent or in a mixture of the two. Generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol or acetonitrile is desirable, where practicable. Lists of additional suitable salts can be found, e.g., in "Remington's Pharmaceutical Sciences", 20th ed., Mack Publishing Company, Easton, Pa., (1985); and in "Handbook of Pharmaceutical Salts: Properties, Selection and Use" by Stahl and Wermuth (Wiley- VCH, Weinheim, Germany, 2002).

In one embodiment, when such pharmaceutical compositions are for human administration, particularly for invasive routes of administration (i.e., routes, such as injection or implantation, that circumvent transport or diffusion through an epithelial barrier), the aqueous solution is pyrogen-free or substantially pyrogen-free. The excipients can be chosen, for example, to effect delayed release of an agent or to selectively target one or more cells, tissues or organs. The pharmaceutical composition can be in dosage unit form such as tablet, capsule (including sprinkle capsule and gelatin capsule), granule, lyophile for reconstitution, powder, solution, syrup, suppository, injection or the like. The composition can also be present in a transdermal delivery system, e.g., a skin patch. The composition can also be present in a solution suitable for topical administration, such as an eye drop.

The term "cancer" is used throughout the specification to refer to the pathological process that results in the formation and growth of a cancerous or malignant neoplasm, i.e., abnormal

tissue that grows by cellular proliferation, often more rapidly than normal and continues to grow after the stimuli that initiated the new growth cease. Malignant neoplasms show partial or complete lack of structural organization and functional coordination with the normal tissue and most invade surrounding tissues, metastasize to several sites and are likely to recur after attempted removal and to cause the death of the patient unless adequately treated. As used herein, the term neoplasia is used to describe all cancerous disease states and embraces or encompasses the pathological process associated with malignant hematogenous, ascitic and solid tumors. Exemplary cancers which may be treated by the present compounds include, but not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Head and neck: squamous cell carcinomas of the head and neck, laryngeal and hypopharyngeal cancer, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, salivary gland cancer oral and oropharyngeal cancer; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma, non-small cell lung cancer), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Colon: colorectal cancer, adenocarcinoma, gastrointestinal stromal tumors, lymphoma, carcinoids, Turcot Syndrome; Gastrointestinal: gastric cancer, gastroesophageal junction adenocarcinoma, esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Breast: metastatic breast cancer, ductal carcinoma in situ, invasive ductal carcinoma, tubular carcinoma, medullary carcinoma, mucinous carcinoma, lobular carcinoma in situ, triple negative breast cancer; Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia, renal cell carcinoma), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma, urothelial carcinoma), prostate (adenocarcinoma, sarcoma, castrate resistant prostate cancer), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma), clear cell carcinoma, clear cell renal cell carcinoma, non-clear cell renal cell carcinoma, papillary carcinoma; Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma),

fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochrondroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Thyroid: medullary thyroid cancer, differentiated thyroid cancer, papillary thyroid cancer, follicular thyroid cancer, Hurthle cell cancer and anaplastic thyroid cancer; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial cancer), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma], fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. Thus, the term “cancerous cell” as provided herein, includes a cell afflicted by any one of the above-identified conditions.

The term “stereoisomers” refers to any enantiomers, diastereoisomers or geometrical isomers of the compound of formula (I), wherever they are chiral or when they bear one or more double bonds. When the compounds of the formula (I) and related formulae are chiral, they can exist in racemic or in optically active form. It should be understood that the invention encompasses all stereochemical isomeric forms, including diastereomeric, enantiomeric and epimeric forms, as well as *d*-Isomers and *l*-Isomers and mixtures thereof. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centres or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, direct separation of enantiomers on chiral chromatographic columns or any other appropriate method known in the art. Starting

compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art. Additionally, the compounds of the present invention may exist as geometric Isomers. The present invention includes all cis, trans, syn, anti, entgegen (E) and zusammen (Z) Isomers as well as the appropriate mixtures thereof.

The term "enantiomers" refers to a pair of stereoisomers which are non-superimposable mirror images of one another. The term "enantiomer" refers to a single member of this pair of stereoisomers. The term "racemic" refers to a 1: 1 mixture of a pair of enantiomers. The disclosure includes enantiomers of the compounds described herein. Each compound herein disclosed includes all the enantiomers that conform to the general structure of the compound. The compounds may be in a racemic or enantiomerically pure form or any other form in terms of stereochemistry. In some embodiment the compounds are the (R, S)-enantiomer.

The term "diastereomers" refers to the set of stereoisomers which cannot be made superimposable by rotation around single bonds. For example, cis- and trans- double bonds, endo- and exo- substitution on bicyclic ring systems and compounds containing multiple stereogenic centres with different relative configurations are considered to be diastereomers. The term "diastereomer" refers to any member of this set of compounds. In some examples presented, the synthetic route may produce a single diastereomer or a mixture of diastereomers. The disclosure includes diastereomers of the compounds described herein.

The compounds of the present invention may be used as single drug or as a pharmaceutical composition in which the compound is mixed with various pharmacologically acceptable excipients.

The compounds of the invention are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared using procedures well known in the pharmaceutical art and comprise at least one compound of the invention. The pharmaceutical composition of the present patent application comprises one or more compounds described herein and one or more pharmaceutically acceptable excipients. Typically, the pharmaceutically acceptable excipients are approved by regulatory authorities or are generally regarded as safe for human or animal use. The pharmaceutically acceptable excipients include, but are not limited to, carriers, diluents, glidants and lubricants, preservatives, buffering agents, chelating agents, polymers, gelling agents, viscosifying agents and solvents.

The pharmaceutical composition can be administered by oral, parenteral or inhalation routes. Examples of the parenteral administration include administration by injection, percutaneous, transmucosal, transnasal and transpulmonary administrations.

Examples of suitable carriers include, but are not limited to, water, salt solutions, alcohols, polyethylene glycols, peanut oil, olive oil, gelatin, lactose, terra alba, sucrose, dextrin, magnesium carbonate, sugar, amylose, magnesium stearate, talc, agar, pectin, acacia, stearic acid, lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, fatty acid esters and polyoxyethylene.

The pharmaceutical composition may also include one or more pharmaceutically acceptable auxiliary agents, wetting agents, suspending agents, preserving agents, buffers, sweetening agents, flavouring agents, colorants or any combination of the foregoing.

The pharmaceutical compositions may be in conventional forms, for example, tablets, capsules, solutions, suspensions, injectables or products for topical application. Further, the pharmaceutical composition of the present invention may be formulated so as to provide desired release profile.

Administration of the compounds of the invention, in pure form or in an appropriate pharmaceutical composition, can be carried out using any of the accepted routes of administration of pharmaceutical compositions. The route of administration may be any route which effectively transports the active compound of the patent application to the appropriate or desired site of action. Suitable routes of administration include, but are not limited to oral, nasal, buccal, dermal, intradermal, transdermal, parenteral, rectal, subcutaneous, intravenous, intraurethral, intramuscular or topical.

Solid oral formulations include, but are not limited to, tablets, capsules (soft or hard gelatin), dragees (containing the active ingredient in powder or pellet form), troches and lozenges.

Liquid formulations include, but are not limited to, syrups, emulsions and sterile injectable liquids, such as suspensions or solutions.

Topical dosage forms of the compounds include ointments, pastes, creams, lotions, powders, solutions, eye or ear drops, impregnated dressings and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration.

The pharmaceutical compositions of the present patent application may be prepared by conventional techniques known in literature.

Suitable doses of the compounds for use in treating the disease or disorder described herein can be determined by those skilled in the relevant art. Therapeutic doses are generally identified through a dose ranging study in humans based on preliminary evidence derived from the animal studies. Doses must be sufficient to result in a desired therapeutic benefit without causing unwanted side effects. Mode of administration, dosage forms and suitable

pharmaceutical excipients can also be well used and adjusted by those skilled in the art. All changes and modifications are envisioned within the scope of the present patent application.

According to one embodiment, the compounds of the present invention can also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the present invention also embraces isotopically-labeled variants of the present invention which are identical to those recited herein, but for the fact that one or more atoms of the compound are replaced by an atom having the atomic mass or mass number different from the predominant atomic mass or mass number usually found in nature for the atom. All isotopes of any particular atom or element as specified are contemplated within the scope of the compounds of the invention and their uses. Exemplary isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, chlorine and iodine, such as ^{2}H ("D"), ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I and ^{125}I. Isotopically labeled compounds of the present inventions can generally be prepared by following procedures analogous to those disclosed in the schemes and/or in the examples herein below, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

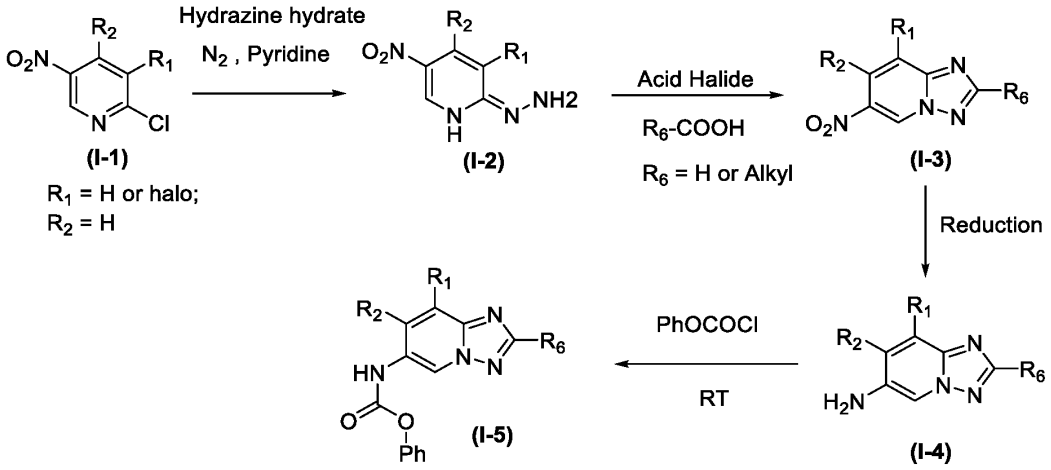
EXPERIMENTAL

The following abbreviations refer respectively to the definitions below:

DMSO – Dimethyl sulfoxide; DPPA - Diphenylphosphoryl azide; DIPEA - N,N-Diisopropylethylamine; $NaHCO_3$ – Sodium bicarbonate; EtOH – Ethanol; MeOH – Methanol; THF – Tetrahydrofuran; $SOCl_2$ – Thionyl chloride; LAH – Lithium aluminium hydride; NaH – Sodium hydride; MnO_2 – Manganese dioxide; IPA – Isopropyl alcohol; $NaBH_4$ – Sodium borohydride; KO^tBu – Potassium tert-butoxide; TFA – Trifluoroacetic acid; TBSOTf – tert-Butyldimethylsilyl trifluoromethanesulfonate; TBAI – Tetra-butyl ammonium iodide; K_2CO_3 – Potassium carbonate; EDCI – 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide; DMAP – 4-Dimethylaminopyridine; PBr_3 – Phosphorous tribromide; NH_4OAc – Ammonium acetate; TMSOTf – Trimethylsilyl trifluoromethanesulfonate; $Pd(dppf)Cl_2$ – [1,1'-Bis(diphenylphosphino)ferrocene]palladium(II) dichloride; Cs_2CO_3 – Caesium carbonate; OsO_4 – Osmium tetroxide; $NaIO_4$ – Sodium per iodate; CBr_4 – Carbon tetra bromide; PPh_3 – Triphenyl phosphine; $Pd_2(dba)_3$ – Tris(dibenzylideneacetone)dipalladium(0); dppf – 1,1'-Bis(diphenylphosphino)ferrocene; $Zn(CN)_2$ – Zinc cyanide; CuI – Copper Iodide; DMEDA – *N*,*N*'-Dimethylethylenediamine; HATU – 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-

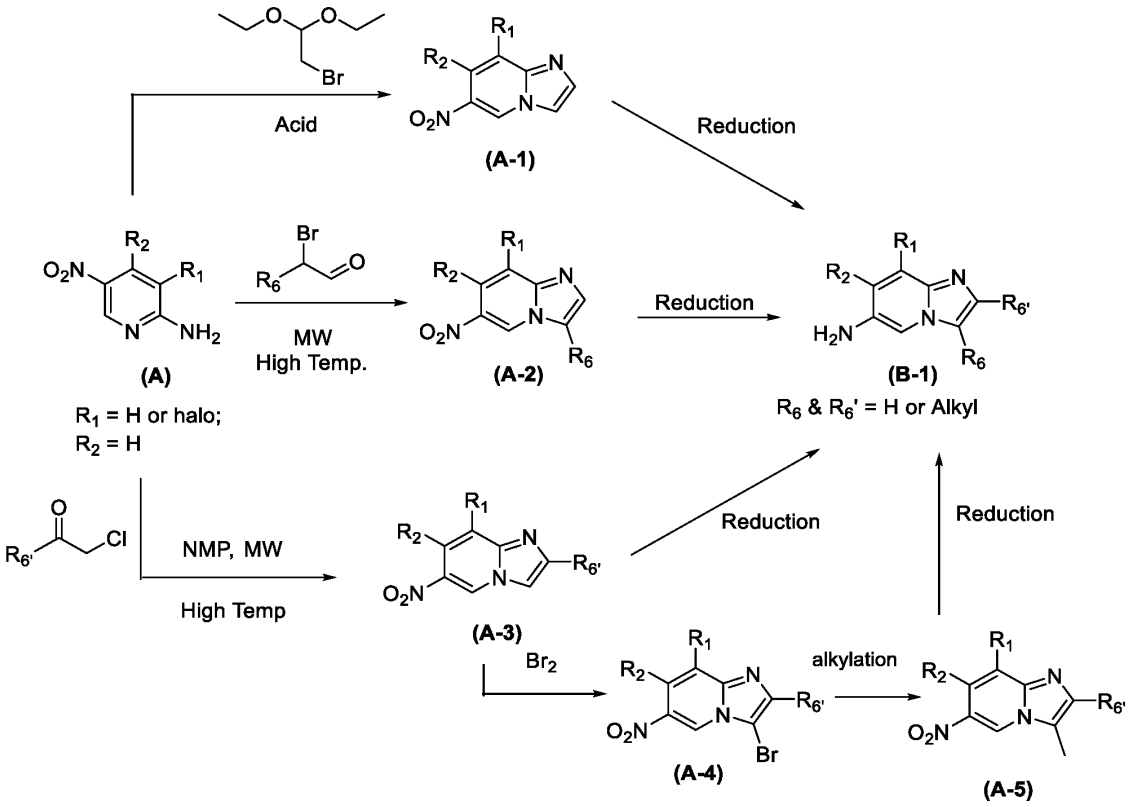
triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate; NH_4Cl – Ammonium chloride; Al_2O_3 – Aluminium oxide; Zn – Zinc; NBS – N-Bromosuccinimide; AIBN – azobisisobutyronitrile; CCl_4 – Carbon tetrachloride; DME – Dimethoxy ethane; $P(Cy)_3$ – Tricyclohexylphosphine; $Pd(OAc)_2$ – Palladium(II) acetate ; K_3PO_4 – Tripotassium phosphate; CDI – 1,1'-Carbonyldiimidazole; KI – Potassium iodide; NaOEt – Sodium ethoxide; $(Boc)_2O$ – Di-tert-butyl dicarbonate; MeI – Methyl iodide; Sphos - Dicyclohexyl(2′,6′-dimethoxy[1,1′-biphenyl]-2-yl)phosphane; Dioxane.HCl; – Hydrochloric acid in dioxane; Na_2SO_4 – Sodium sulphate; Na_2CO_3 – Sodium carbonate; $Na_2S_2O_3$-sodium thiosulphate; H_2O – water; br – Broad; Å– Angstrom ; °C - Degree Celsius ; conc – Concentrated; $CHCl_3$ – Chloroform; $CDCl_3$//chloroform-d- Deuterated Chloroform; DMSO-d_6- Deuterated dimethyl sulfoxide; CH_2Cl_2 - DCM – Dichloromethane; DMF- *N, N*- Dimethylformamide;; Et_2O – Diethyl ether; g- Gram; h – Hours; ^1H- Proton; HCl- Hydrochloric acid; Hz- Hertz; *J* - Coupling Constant; LC–MS - Liquid Chromatography- Mass Spectroscopy; HPLC - High-performance liquid chromatography; chiral HPLC - chiral high-performance liquid chromatography; M – Molar; MHz – Mega Hertz (frequency); MS - Mass Spectroscopy; mmol - millimole; mL - millilitre; min – Minutes; mol – Moles; M^+- Molecular ion; m/z-mass to charge ratio; N - Normality; NMR - Nuclear Magnetic Resonance; Et_3N/TEA – Triethylamine; ppm - Parts per million; rt/RT – Room temperature; s – Singlet; d – Doublet, t – Triplet; q – Quartet; m – Multiplet; dd – doublet of doublets; td – triplet of doublets; qd – quartet of doublets; ddd – doublet of doublets of doublets; dt – doublet of triplets; ddt – doublet of doublets of triplets; p-pentet; TLC - Thin Layer Chromatography; THF – Tetrahydrofuran; % - Percentage; µ - micro; µL-microliter and δ - Delta; anh. – anhydrous. ±-racemic mixture; SFC –Supercritical fluid chromatography.

General Scheme - I



The general scheme for the synthesis of compound represented by formula (I-5) is depicted in above scheme. The compound of formula (I-2) can be obtained from compound of formula (I-1) by reacting with hydrazine in appropriate solvent under nitrogen atmosphere at a room temperature. Compound of formula (I-2) can be reacted with acid(R_6-COOH) or ester thereof at high temperature to result in compound of formula (I-3) which upon reduction in the presence of iron can yield a compound of formula (I-4). Further, formula (I-4) compounds can be reacted with phenyl chloroformate in appropriate solvents to give compound of formula (I-5).

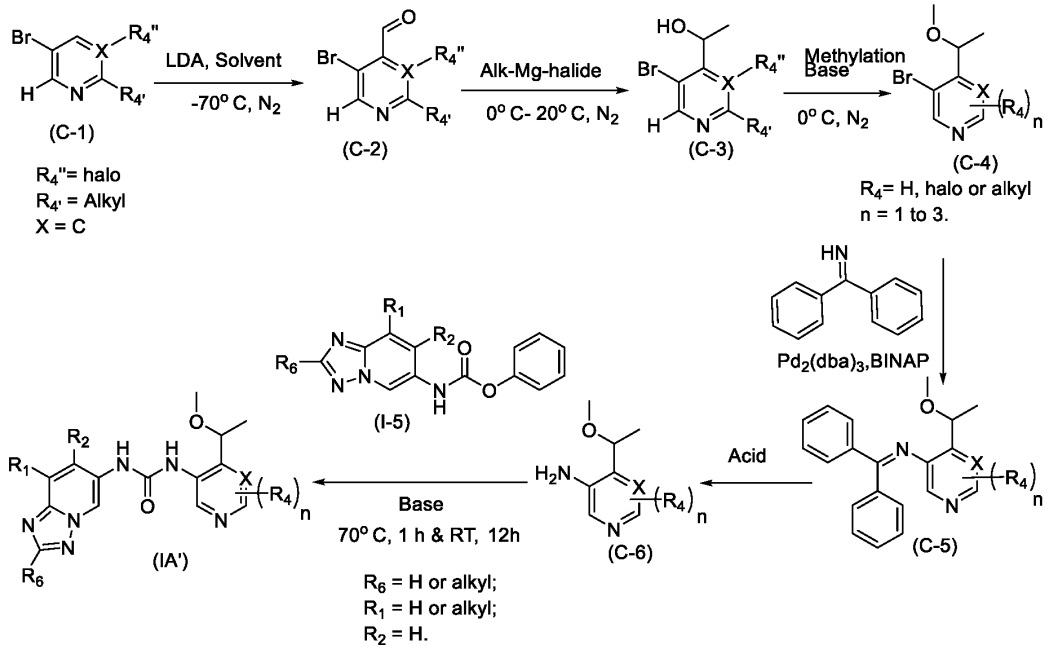
General Scheme - II



The general scheme for the synthesis of compound represented by formula (B-1) is depicted in above scheme. The compound of formulas (A-1), (A-2) and (A-3) can be obtained from compound of formula (A)) by reacting with respective halogen derivatives in appropriate reaction conditions. The compound of formulas (A-1), (A-2) and (A-3) can individually be subjected to reduction in the presence of metal to yield compounds represented by formula (B-

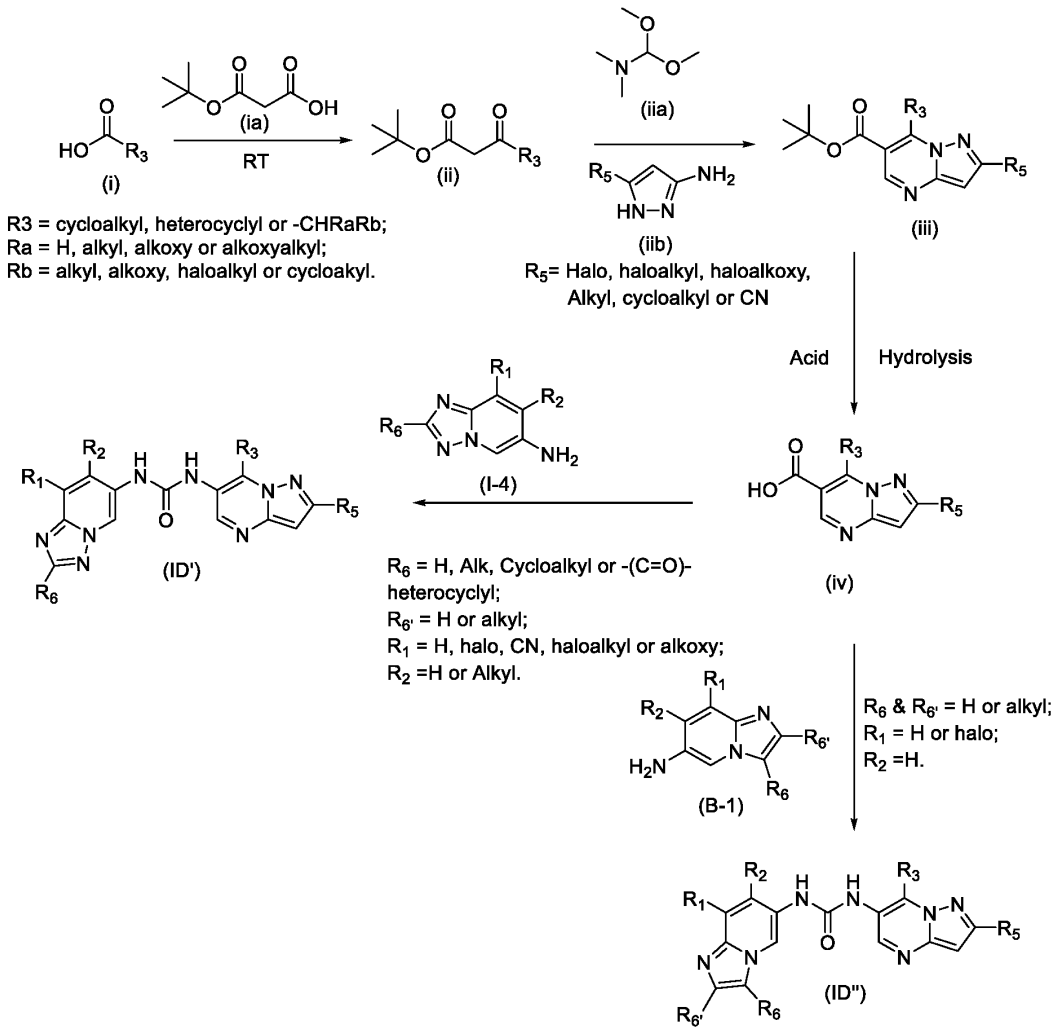
1). Moreover, the compound of formula (A-3), upon bromination and further alkylation can result in compounds represented by formula (B-1).

General Scheme - III



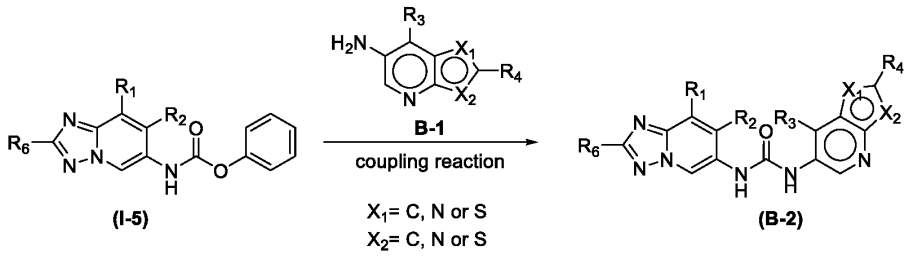
The general scheme for the synthesis of compound represented by formula (IA) is depicted in above scheme. The compound of formula (C-2) can be obtained from compound of formula (C-1) by reacting with a strong base in an appropriate solvent under nitrogen atmosphere. Compound of formula (C-2) can be reacted with alkyl magnesium halide under nitrogen atmosphere to result in compound of formula (C-3) which upon methylation in the presence of a base under nitrogen atmosphere can yield compound of formula (C-4). The formula (C-4) compounds can be reacted with benzhydrylimine to give compound of formula (C-5). Further compound of formula (C-5) upon treatment with an appropriate acid can yield compound of formula (C-6). Further, compound of formula (C-6) while reacting with compound of formula (I-5) in the presence of a base can give compound of formula (IA') as a product.

General Scheme - IV



The general scheme for the synthesis of compounds of formula (ID') is depicted in above scheme. The compound of formula (ii) can be obtained from compound of formula (i) by reacting with formula (ia) in an appropriate solvent at room temperature. Compound of formula (ii) can be reacted with corresponding derivatives of formula (iib) and (iia) at the temperature ranging between 80°C to 140°C to result in compound of formula (iii) which can be further hydrolysed in the presence of an acid to yield compound of formula (iv). Compound of formula (iv) under the reaction conditions of Curtius rearrangement with formula (I-4) or formula (B-1) can give compound of formula (ID') or formula (ID'') respectively.

General Scheme - V

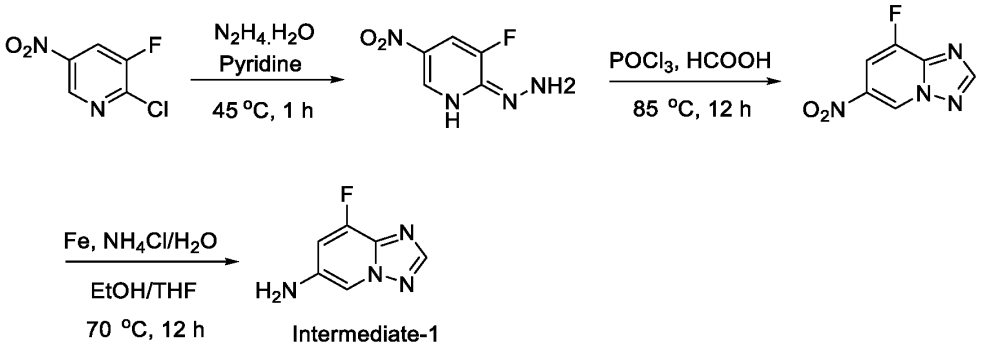


X_1= C, N or S
X_2= C, N or S

R_1 = H or alkyl;
R_2 = H.
R_3= H, alkyl, halo, haloalkyl, cycloalkyl or CHR_aR_b
R_4= H, alkyl or halo.
R_6 = H or alkyl
R_aR_b= H, alkoxy, haloalkyl or halo.

The general scheme for the synthesis of compound represented by formula (B-2) is depicted in above scheme. The compound of formula (B-2) can be obtained by reacting compound of formula (I-5) and compound of formula (B-1) in the presence of coupling reagent to give compound of formula (B-2).

Intermediate-1: 8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-6-amine



Step-a: Synthesis of (E)-3-fluoro-2-hydrazineylidene-5-nitro-1,2-dihydropyridine

To a stirred solution of 2-chloro-3-fluoro-5-nitropyridine (10.0 g, 56.648 mmol) in Pyridine (50.0 mL), was added hydrazine hydrate (80%) (4.249 g, 84.980 mmol) under nitrogen atmosphere at room temperature, then the reaction mixture was stirred at 45 °C for 1h. The mixture was concentrated, co-distilled with methanol and concentrated. The obtained residue was washed with n-pentane and dried under reduced pressure to afford 16.5 g of (E)-3-fluoro-2-hydrazineylidene-5-nitro-1,2-dihydropyridine. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.73 (d, J = 1.2 Hz, 1H), 7.72 (dd, J = 12 Hz, J = 11.6 Hz, 1H), 6.27 (bs, 2H).; M/z = 173.10 $[M+H]^+$.

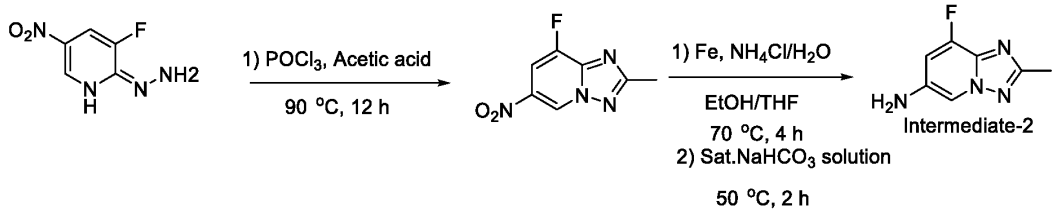
Step-b: Synthesis of 8-fluoro-6-nitro-[1,2,4]triazolo[1,5-a]pyridine

To a stirred solution of (E)-3-fluoro-2-hydrazineylidene-5-nitro-1,2-dihydropyridine (8.0 g, 46.478 mmol) in $POCl_3$ (10 ml) was added formic acid (3.209 g, 69.718 mmol) then the reaction mixture was stirred at 85 °C for 12 h. The reaction mixture was concentrated, and the obtained residue was dissolved in ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution, brine solution, dried over sodium sulphate and concentrated under reduced pressure to afford 5 g of 8-fluoro-3-methyl-6-nitro-[1,2,4] triazolo[4,3-a]pyridine. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.18 (s, 1H), 8.89 (s, 1H), 8.5 (d, J = 8 Hz, 1H).; M/z = 183.0 $[M+H]^+$.

Step-c: Synthesis of 8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-6-amine

To a stirred solution of 8-fluoro-6-nitro-[1,2,4]triazolo[1,5-a]pyridine (4.7 g, 25.809 mmol) in a mixture of solvents ethanol and THF (50.0 mL, 1:1 ratio), were added ammonium chloride (6.968 g, 129.040 mmol) in water (25.0 mL) and Iron (7.207 g, 129.040 mmol). The reaction mixture was stirred for 12 hours at 70 °C. The reaction mixture was diluted with ethyl acetate and filtered through a Celite® bed. The organic layer was separated from the aqueous layer and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure to give 3.0 g of 8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-6-amine. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.25 (s, 1H), 7.93 (d, J = 1.2 Hz, 1H), 7.22 (m, 1H), 5.41 (bs, 2H).; LCMS: 153.1 $[M+H]^+$.

Intermediate-2: 8-fluoro-2-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-amine



Step-a: Synthesis of 8-fluoro-2-methyl-6-nitro-[1,2,4]triazolo[1,5-a]pyridine

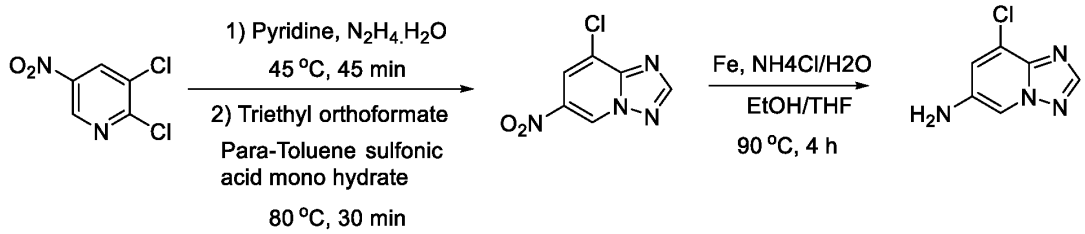
To a stirred solution of (E)-3-fluoro-2-hydrazineylidene-5-nitro-1,2-dihydropyridine (10.0 g, 58.098. mmol) in $POCl_3$ (80 ml), was added acetic acid (5.233 g, 87.147 mmol) and the reaction mixture was stirred at 90 °C for 12 h. Then the mixture was concentrated. The obtained residue was diluted with ethyl acetate. The organic layer was washed with sodium bicarbonate solution, brine solution, dried over sodium sulphate and concentrated to afford mixture of 8-fluoro-2-methyl-6-nitro-[1,2,4]triazolo[1,5-a]pyridine and 8-fluoro-3-methyl-6-nitro-[1,2,4]triazolo[4,3-a]pyridine. The obtained residue was diluted with Sat. NaHCO3 solution and stirred for 2h at 50°C. The reaction mixture was extracted with ethyl acetate and

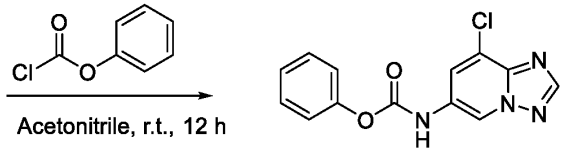
the organic layer was washed with water, brine, dried over sodium sulphate and concentrated to afford 4.5 g (39.49%) of 8-fluoro-2-methyl-6-nitro-[1,2,4]triazolo[1,5-a]pyridine. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.01 (d, J = 1.6 Hz, 1H), 8.41-8.37 (m, 1H), 2.54 (s, 3H).; M/z = 197.0 [M+H].

Step-b: Synthesis of 8-fluoro-2-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-amine

To a stirred solution of 8-fluoro-3-methyl-6-nitro-[1,2,4] triazolo[4,3-a]pyridine (4.5 g, 22.943 mmol) in ethanol (40 mL) were added THF (40.0 mL), ammonium chloride (9.204 g, 172.070 mmol) in water (40.0 mL) and iron (9.610 g, 172.070 mmol). The reaction mixture was stirred for 4 hours at 70 °C. The reaction mixture was diluted with ethyl acetate and filtered through Celite® bed. The organic layer was separated from the aqueous layer and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure to give 3 g of 8-fluoro-3-methyl-[1,2,4]triazolo[4,3-a]pyridin-6-amine. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.79 (s, 1H), 7.00 (d, J = 12 Hz, 1H), 5.27 (bs, 2H), 2.33 (s, 3H).; LCMS: 167.10 $[M+H]^+$

Intermediate-3: phenyl (8-chloro-[1,2,4]triazolo[1,5-a]pyridin-6-yl)carbamate





Intermediate-3

Step-a: Synthesis of 8-chloro-6-nitro-[1,2,4]triazolo[1,5-a]pyridine

To a stirred solution of 2,3-dichloro-5-nitropyridine (3.0 g, 15.545 mmol) in pyridine (8 mL), was added hydrazine hydrate (80%) (2.334 g, 46.620 mmol) at room temperature then the reaction mixture was stirred at 45 °C for 45 min. The mixture was concentrated, co-distilled with methanol and concentrated. The obtained residue was washed with n-pentane and dried under reduced pressure. To this residue added ethyl orthoformate (8.249 g, 77.730 mmol) and para-toluene sulfonic acid monohydrate (2.957 g, 15.540). The reaction mixture was stirred at

80 °C for 30 min. The reaction mixture was diluted with ethyl acetate and the organic layer was washed with water, brine solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford 3.0 g of 8-chloro-6-nitro-[1,2,4]triazolo[1,5-a]pyridine. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.24 (d, J = 1.6 Hz, 1H), 8.88 (s, 1H), 8.64 (d, J = 2.0 Hz, 1H).; M/z = 199.10 [M+H] $^+$

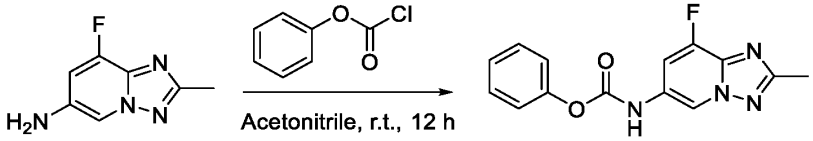
Step-b: Synthesis of 8-chloro-[1,2,4]triazolo[1,5-a]pyridin-6-amine

To a stirred solution of 8-chloro-6-nitro-[1,2,4]triazolo[1,5-a]pyridine (1.5 g, 7.554 mmol) in a mixture of solvents ethanol and THF (30.0 mL, 1:1 ratio), were added ammonium chloride (2.020 g, 37.760 mmol) in water (15.0 mL) and iron (2.115 g, 129.040 mmol). The reaction mixture was stirred for 4 hours at 90 °C. The reaction mixture was filtered through a Celite® bed and the filtrate was concentrated. The obtained residue was diluted with ethyl acetate. The organic layer was washed with water, brine solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford 0.7 g of 8-chloro-[1,2,4]triazolo[4,3-a]pyridin-6-amine. LCMS: 169.0 [M+H] $^+$

Step-c: Synthesis of phenyl (8-chloro-[1,2,4]triazolo[4,3-a]pyridin-6-yl)carbamate

To a stirred solution of 8-chloro-[1,2,4]triazolo[4,3-a]pyridin-6-amine (0.5 g, 2.96 mmol) in 10 mL of acetonitrile, was added phenyl chloroformate (0.55 g, 3.55 mmol). The reaction mixture was stirred for 12 hours at room temperature. The reaction mixture was diluted with water, and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated $NaHCO_3$ solution, water, brine solution, dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure. The residue obtained was purified by column chromatography (SiO_2, 30-40% EtOAc in Hexane) to give 0.5 g (58.39%) of phenyl (8-chloro-[1,2,4]triazolo[4,3-a]pyridin-6-yl)carbamate. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.71 s, 1H), 9.08 (d, 1H), 8.54 (s, 1H), 7.86 (d, J = 1.2 Hz, 1H), 7.48-7.44 (t, 2H), 7.31-7.26 (m, 3H).; LCMS: 289.0 [M+H] $^+$.

Intermediate-4: phenyl (8-fluoro-2-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)carbamate

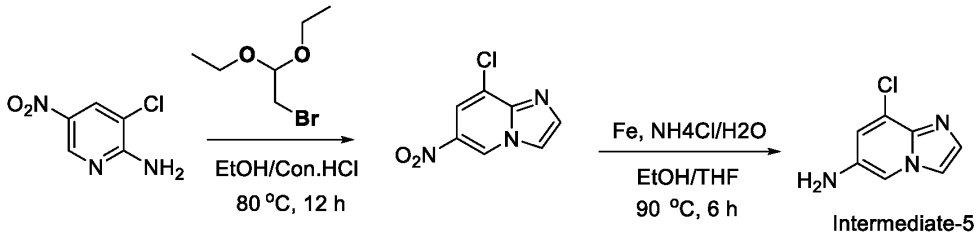


Intermediate-2 Intermediate-4

To a stirred solution of 8-fluoro-2-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-amine (0.15 g, 0.903 mmol) in 4 mL of acetonitrile, was added phenyl chloroformate (0.212 g, 1.355 mmol). The reaction mixture was stirred for 12 hours at room temperature. The reaction mixture was

diluted with water, extracted with ethyl acetate. The ethyl acetate layer was washed with saturated $NaHCO_3$ solution, water, brine solution, dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure. The residue obtained was purified by column chromatography (SiO_2, 30-40% EtOAc in Hexane) to give 0.16 g (61.90%) of phenyl (8-fluoro-2-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)carbamate. ^1H NMR (400 MHz, DMSO-d6) δ 10.65 (s, 1H), 8.88 (s, 1H), 7.56 (d, J = 11.6 Hz, 1H), 7.47-7.43 (t, 2H), 7.31-7.25 (m, 3H), 2.47 (s, 3H).; LCMS: 287.1 $[M+H]^+$.

Intermediate-5: 8-chloroimidazo[1,2-a]pyridin-6-amine



Intermediate-5

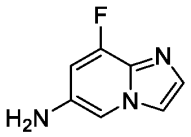
Step-a: Synthesis of 8-chloro-6-nitroimidazo[1,2-a]pyridine

To a stirred solution of 3-chloro-5-nitropyridin-2-amine (1.5 g, 8.643 mmol) in EtOH (30 mL) was added concentrated HCl (10.0 ml) and 2-bromo-1,1-diethoxyethane (8.516 g, 43.215 mmol), then the reaction mixture was stirred at 80 °C for 12h. The mixture was cooled to 0 °C, precipitated solid was filtered, washed with cold EtOH, and dried under reduced pressure to afford 0.86 g (56%) of 8-chloro-6-nitroimidazo[1,2-a]pyridine. M/z = 198.10 $[M+H]^+$

Step-b: Synthesis of 8-chloroimidazo[1,2-a]pyridin-6-amine

To a stirred solution of 8-chloro-6-nitroimidazo[1,2-a]pyridine (0.8 g, 4.049 mmol) in a mixture of solvents Ethanol and THF (30.0 mL, 1:1 ratio), were added ammonium chloride (2.168 g, 40.409 mmol) in water (15.0 mL) and iron (2.261 g, 40.409 mmol). The reaction mixture was stirred for 6 hours at 90 °C. The reaction mixture was diluted with ethyl acetate and filtered through Celite® bed. The organic layer was separated from the aqueous layer and extracted with ethyl acetate. The combined organic layers were washed with brine solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford 0.2 g (29.47%) of 8-chloroimidazo[1,2-a]pyridin-6-amine. LCMS: 168.10 $[M+H]^+$

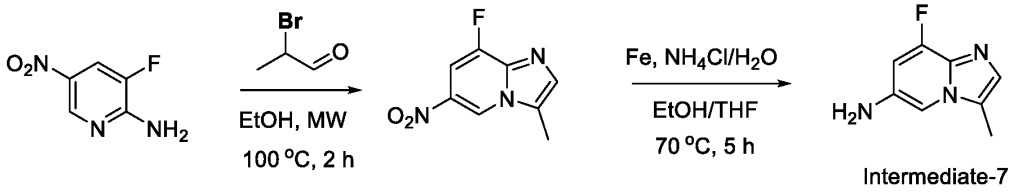
Intermediate-6: 8-fluoroimidazo[1,2-a]pyridin-6-amine



Intermediate-6

The compound of intermediate 6 was prepared by the similar procedure in Intermediate 5 with appropriate variations in reactants, quantities of reagents, solvents, and reaction conditions. Yield: 0.5 g. M/z = 152.10 $[M+H]^+$

Intermediate-7: 8-fluoro-3-methylimidazo[1,2-a]pyridin-6-amine



Intermediate-7

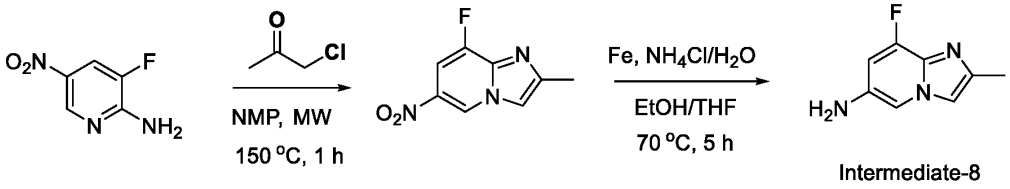
Step-a: Synthesis of 8-fluoro-3-methyl-6-nitroimidazo[1,2-a]pyridine

To the microwave vial (MW), were added 3-fluoro-5-nitropyridin-2-amine (0.5 g, 3.161 mmol), 2-bromopropanal (2.252 g, 16.442 mmol) and EtOH (10 mL) and subjected to microwave at 100 °C for 2 hours. The mixture was concentrated under reduced pressure. The residue obtained was purified by column chromatography (SiO_2, 30-40% EtOAc in hexane) to afford 0.13 g (21.07%) of 8-fluoro-3-methyl-6-nitroimidazo[1,2-a]pyridine. LCMS: 196.1 $[M+H]^+$.

Step-b: Synthesis of 8-fluoro-3-methylimidazo[1,2-a]pyridin-6-amine

To a stirred solution of 8-fluoro-3-methyl-6-nitroimidazo[1,2-a]pyridine (0.1 g, 0.512 mmol) in a mixture of solvents ethanol and THF (18.0 mL, 1:1 ratio), were added ammonium chloride (0.164 g, 3.070 mmol) in water (8.0 mL) and iron (0.172 g, 3.070 mmol). The reaction mixture was stirred for 5 hours at 70 °C. The reaction mixture was filtered through Celite® bed and filtrate was concentrated. The obtained residue was diluted with ethyl acetate. The organic layer was washed with water, brine solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford 0.065 g of 8-fluoro-3-methylimidazo[1,2-a]pyridin-6-amine. LCMS: 166.1 $[M+H]^+$.

Intermediate-8: 8-fluoro-2-methylimidazo[1,2-a]pyridin-6-amine



Intermediate-8

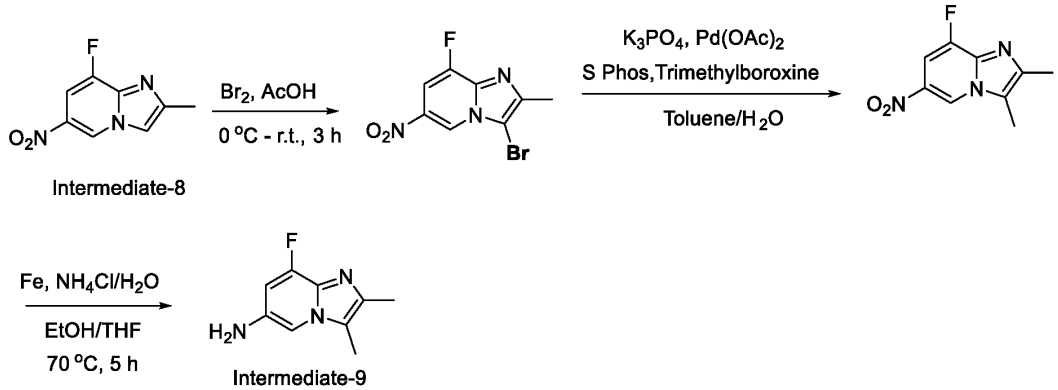
Step-a: Synthesis of 8-fluoro-2-methyl-6-nitroimidazo[1,2-a]pyridine

To the sealed tube, added 3-fluoro-5-nitropyridin-2-amine (1.0 g, 6.365 mmol), 1-chloropropan-2-one (0.648 g, 7.001 mmol) and NMP (10 mL) was subjected to microwave at 150 °C for 1 hours. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed brine solution, dried over anhydrous sodium sulphate, and concentrated under reduced pressure. The residue obtained was purified by column chromatography (SiO_2, 30-50% EtOAc in Hexane) to afford 0.35 g (28.18%) of 8-fluoro-2-methyl-6-nitroimidazo[1,2-a]pyridine. LCMS: 196.1 $[M+H]^+$.

Step-b: Synthesis of 8-fluoro-2-methylimidazo[1,2-a]pyridin-6-amine

To a stirred solution of 8-fluoro-2-methyl-6-nitroimidazo[1,2-a]pyridine (0.35 g, 1.792 mmol) in a mixture of solvents ethanol and THF (20.0 mL, 1:1 ratio), were added ammonium chloride (0.575 g, 10.750 mmol) in water (10.0 mL) and iron (0.601 g, 10.750 mmol). The reaction mixture was stirred for 5 hours at 70 °C. The reaction mixture was filtered through Celite® bed and filtrate was concentrated. The obtained residue was diluted with ethyl acetate. The organic layer was washed with water, brine solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford 0.25 g of 8-fluoro-2-methylimidazo[1,2-a]pyridin-6-amine. LCMS: 166.1 $[M+H]^+$.

Intermediate-9: 8-fluoro-2,3-dimethylimidazo[1,2-a]pyridin-6-amine



Intermediate-8

Intermediate-9

Step-a: Synthesis of 3-bromo-8-fluoro-2-methyl-6-nitroimidazo[1,2-a]pyridine

To a stirred solution 8-fluoro-2-methyl-6-nitroimidazo[1,2-a]pyridine (Intermediate-8) (0.5 g, 2.561 mmol) in AcOH (15 mL), was added bromine (0.225 g, 2.810 mmol) at 0 °C then the reaction mixture was allowed to be stirred for 3 hours at room temperature. The mixture was diluted with Ethyl acetate and washed with water, saturated $NaHCO_3$ solution, brine solution, dried over anhydrous sodium sulphate, and concentrated under reduced pressure. The residue obtained was purified by column chromatography (SiO_2, 30-50% EtOAc in Hexane) to afford 0.12 g (17.09%) of 3-bromo-8-fluoro-2-methyl-6-nitroimidazo[1,2-a]pyridine. LCMS: 276.0 $[M+H]^+$.

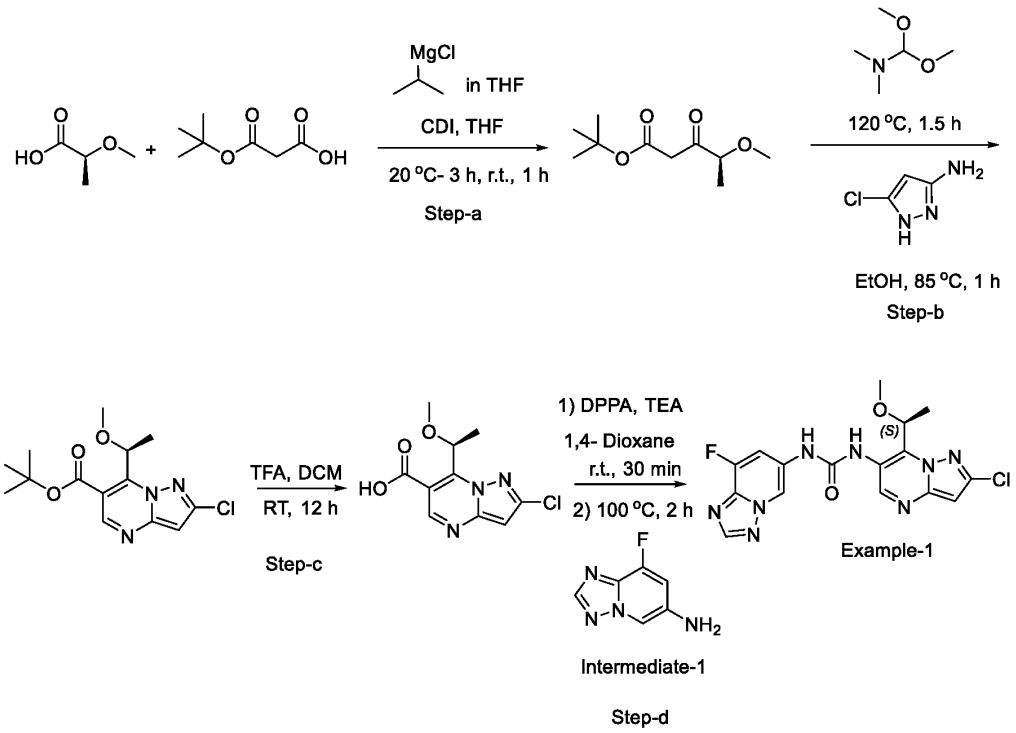
Step-b: Synthesis of 8-fluoro-2,3-dimethyl-6-nitroimidazo[1,2-a]pyridine

To a stirred solution of 3-bromo-8-fluoro-2-methyl-6-nitroimidazo[1,2-a]pyridine (0.110 g, 0.401 mmol) in a toluene (5 mL) were added H_2O (1 mL), K_3PO_4 (0.169, 0.790 mmol), $Pd(OAc)_2$ (0.007, 0.030 mmol), SPhos (0.033, 0.080 mmol) and trimethyl boroxine (0.077, 0.610 mmol) then the reaction mixture was degassed with nitrogen for 5 min, allowed stirred for 8 hours at 80 °C. The reaction mixture was filtered through Celite® bed, the filtrate was concentrated under reduced pressure. The obtained residue was diluted with ethyl acetate. The organic layer was washed with water, brine solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford 0.15 g of 8-fluoro-2,3-dimethyl-6-nitroimidazo[1,2-a]pyridine. LCMS: 210.0 $[M+H]^+$

Step-c: Synthesis of 8-fluoro-2,3-dimethylimidazo[1,2-a]pyridin-6-amine

To a stirred solution of 8-fluoro-2,3-dimethyl-6-nitroimidazo[1,2-a]pyridine (0.15 g, 0.717 mmol) in a mixture of solvents ethanol and THF (12.0 mL, 1:1 ratio), were added ammonium chloride (0.230 g, 4.300 mmol) in water (6.0 mL) and iron (0.240 g, 4.300 mmol). The reaction mixture was stirred for 5 hours at 70 °C. The reaction mixture was filtered through Celite® bed and filtrate was concentrated. The obtained residue was diluted with ethyl acetate. The organic layer was washed with water, brine solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford 0.16 g of 8-fluoro-2,3-dimethylimidazo[1,2-a]pyridin-6-amine. LCMS: 180.10 $[M+H]^+$

Example-1: (S)-1-(2-chloro-7-(1-methoxyethyl) pyrazolo[1,5-a] pyrimidin-6-yl)-3-(8-fluoro-3-methyl-[1,2,4] triazolo[4,3-a] pyridin-6-yl) urea



Step-a: Synthesis of (S)-tert-butyl 4-methoxy-3-oxopentanoate

To a stirred solution of (S)-2-methoxypropanoic acid (5.0 g, 48.026 mmol) in THF (100 mL) at 0 °C was added CDI (8.566 g, 52.820 mmol) and then reaction mixture was stirred for 3 hours under nitrogen atmosphere at room temperature. In a separate flask to a stirred solution of 3-(tert-butoxy)-3-oxopropanoic acid (11.538 g, 72.039 mmol) in 60 mL of THF at 0°C was added dropwise 2M isopropyl magnesium chloride in THF (14.345 g, 139.270 mmol) and the reaction mixture was stirred for 3 hours under nitrogen atmosphere at 20 °C. Then, this solution was added dropwise to the acyl imidazole solution at 0 °C, and the resulting mixture was stirred for 1h at RT. The reaction mixture was quenched with 10% aqueous citric acid (12.5 ml), extracted with AcOEt, washed with aqueous saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated to give 6.83 g of (S)-tert-butyl 4-methoxy-3-oxopentanoate. ^1H NMR (400 MHz, DMSO-d6) δ 3.86-3.84 (q, 1H), 3.508-3.491 (m, 2H), 3.27 (s, 3H), 1.40 (s, 9H), 1.19 (d, J = 6.4 Hz, 3H).

Step-b: Synthesis of (S)-tert-butyl 2-chloro-7-(1-methoxyethyl) pyrazolo[1,5-a] pyrimidine-6-carboxylate

A mixture of (S)-tert-butyl 4-methoxy-3-oxopentanoate (6.830 g, 33.77 mmol) and 1,1-dimethoxy-N, N-dimethylmethanamine (4.024 ml, 33.77 mmol) was stirred at 120 °C for 1.5h. Then, a solution of 5-chloro-1H-pyrazol-3-amine (3.969 g, 33.77 mmol) in EtOH (41 ml) was

added and the reaction mixture was stirred at 85 °C for 1h. The mixture was concentrated, and the crude product was purified by flash column chromatography (SiO_2, 20% EtOAc in Hexane) to afford 6.3 g (59.84%) of (S)-tert-butyl 2-chloro-7-(1-methoxyethyl)pyrazolo[1,5-a] pyrimidine-6-carboxylate. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.64 (s, 1H), 7.02 (s, 1H), 5.26-5.25 (q, 1H), 3.21 (s, 3 H), 1.61 (d, J = 6.4 Hz, 3H), 1.54 (s, 9H).; LCMS: 312.1 [M+H] $^+$

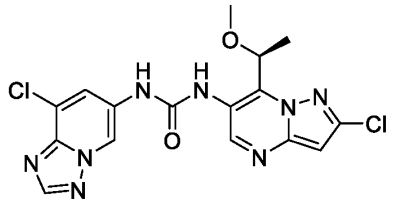
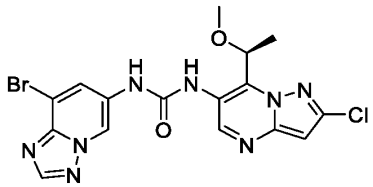
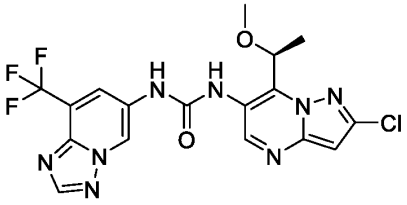
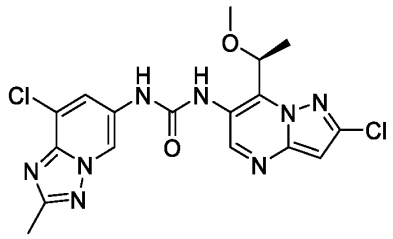
Step-c: Synthesis of (S)-2-chloro-7-(1-methoxyethyl)pyrazolo[1,5-a]pyrimidine-6-carboxylic acid

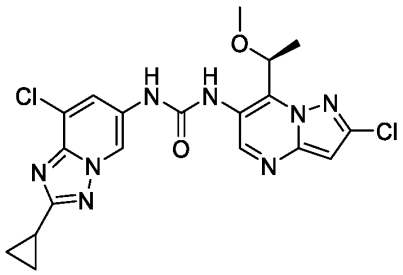
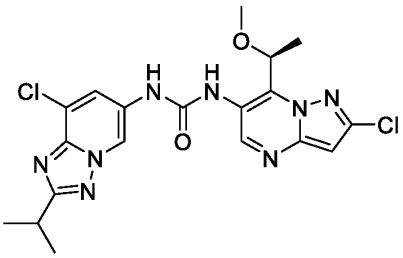
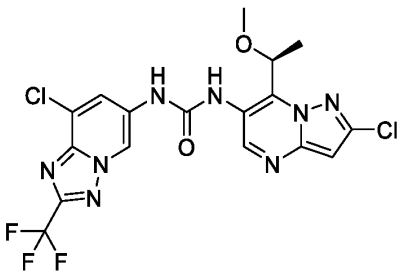
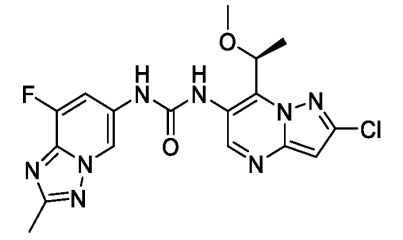
To a stirred solution of (S)-tert-butyl 2-chloro-7-(1-methoxyethyl)pyrazolo[1,5-a] pyrimidine-6-carboxylate (6.30 g, 20.207 mmol) in DCM (30 ml) at RT was added TFA (30 ml). The reaction mixture was stirred 12 h at RT and concentrated. Diethyl ether was added to the residue, triturated and the suspension was evaporated to dryness to afford 4.5 g (crude) of (S)-2-chloro-7-(1-methoxyethyl) pyrazolo[1,5-a] pyrimidine-6-carboxylic acid. ^{1}H NMR (300 MHz, DMSO-d6) δ 8.73 (s, 1H), 7.03 (s, 1H), 5.44-5.37 (q, 1H), 3.20 (s, 3 H), 1.64 (d, J = 6.6 Hz, 3H).; LCMS: 256.10 [M+H] $^+$

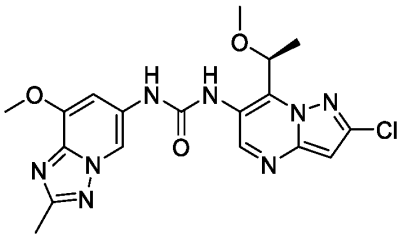
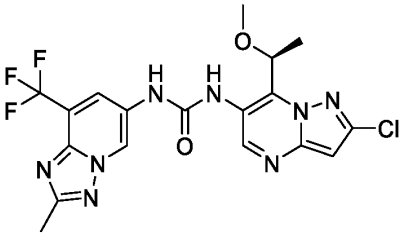
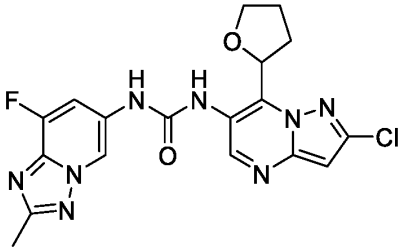
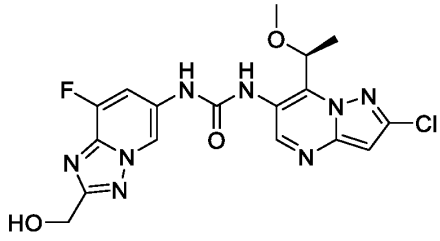
Step-d: Synthesis of (S)-1-(2-chloro-7-(1-methoxyethyl) pyrazolo[1,5-a] pyrimidin-6-yl)-3-(8-fluoro-3-methyl-[1,2,4]triazolo[4,3-a]pyridin-6-yl) urea

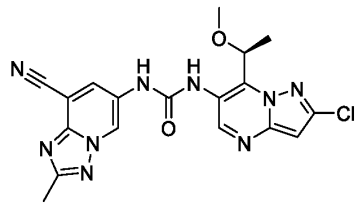
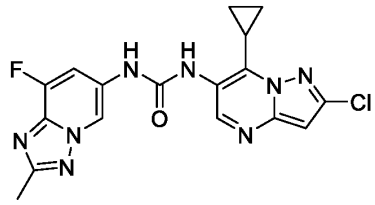
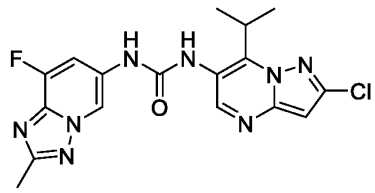
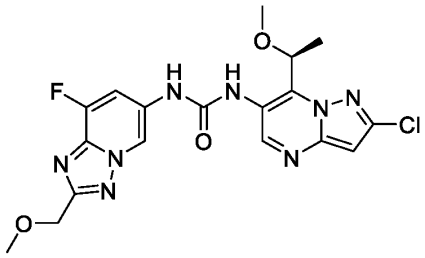
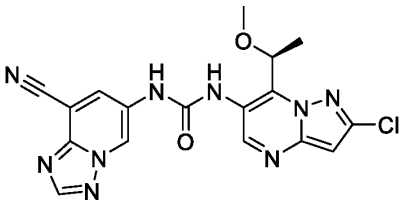
To a stirred solution of (S)-2-chloro-7-(1-methoxyethyl)pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (0.310 g, 0.840 mmol) in dioxane (3 ml) were added DPPA (0.277 g, 1.008 mmol) and TEA (0.425 g, 4.200 mmol). The reaction mixture was stirred at RT for 30 min. Then, 8-fluoro-3-methyl-[1,2,4]triazolo[4,3-a]pyridin-6-amine (0.418 g, 2.520 mmol) in dioxane (3 ml) was added. The reaction mixture was stirred at 100 °C for 2h. The reaction mixture was cooled to RT, evaporated and the residue was dissolved in EtOAc, The organic layer was washed with aq. Sat. $NaHCO_3$ solution, water, brine solution dried over anhydrous Na_2SO_4, filtered, concentrated and purified by flash column chromatography (SiO_2, 10% EtOAc in Hexane) to afford 0.05 g (9.84%) of (S)-1-(2-chloro-7-(1-methoxyethyl) pyrazolo[1,5-a] pyrimidin-6-yl)-3-(8-fluoro-3-methyl-[1,2,4]triazolo[4,3-a]pyridin-6-yl)urea. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.07 (d, J = 1.8 Hz, 1H), 8.88 (s, 1H), 8.47 (s, 1H), 7.54 (d, J = 11.8 Hz, 1H), 6.87 (s, 1H), 5.36 (q, J = 6.6 Hz, 1H), 3.29 (s, 3H), 1.54 (d, J = 6.6 Hz, 3H).; LCMS: 405.0 [M+H] $^+$

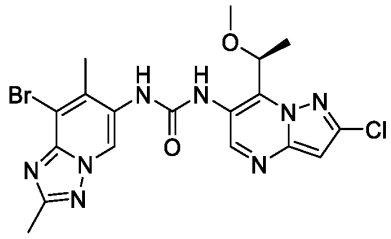
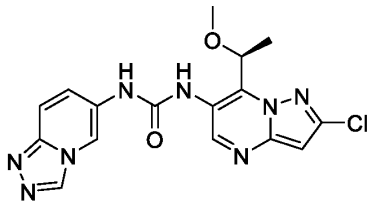
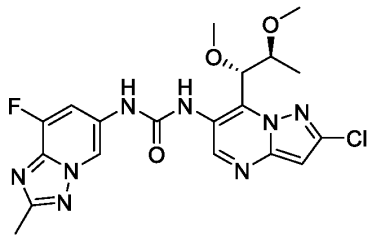
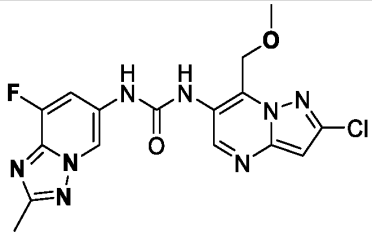
The compounds given in the following table were prepared by procedure similar to the one described in Example-I with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. The physiochemical characteristics of the compounds are summarized in the table below.

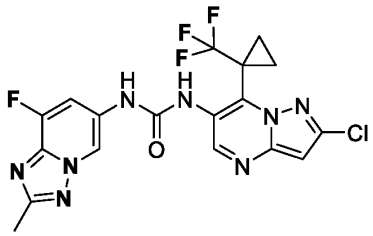
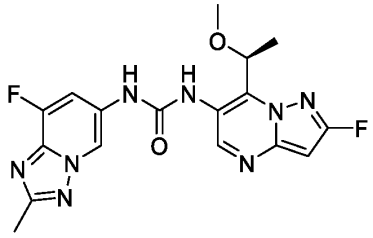
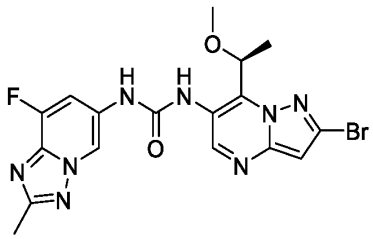
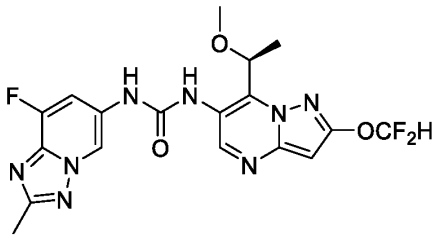
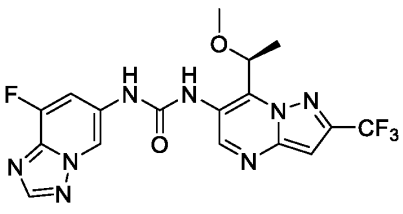
Example	Structure	Analytical data
2		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 9.20 (d, J = 1.8 Hz, 1H), 8.94 (s, 1H), 8.51 (s, 2H), 7.82 (d, J = 1.8 Hz, 1H), 6.94 (s, 1H), 5.42-5.40 (q, 1H), 3.17 (d, J = 5.3 Hz, 1H), 2.08 (s, 3H), 1.59 (d, J = 7.0 Hz, 3H).; LCMS: 423.0 [M+H]$^+$.
3		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 9.22 (s, 1H), 8.94 (s, 1H), 8.50 (s, 2H), 7.96 (s, 1H), 6.94 (s, 1H), 5.33-5.50 (q, 1H), 3.33 (s, 3H), 1.58 (d, J = 6.6 Hz, 3H).; LCMS: 466.9 [M+H]$^+$.
4		^{1}H NMR (400 MHz, DMSO-d_6) δ 10.04 (s, 1H), 9.43 (s, 1H), 8.97 (s, 1H), 8.58 (d, J = 20.6 Hz, 2H), 8.08 (s, 1H), 6.95 (s, 1H), 5.38-5.45 (q, 1H), 3.33 (s, 3H), 1.59 (d, J = 6.6 Hz, 3H).; LCMS: 455.10 [M+H]$^+$.
5		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.81 (s, 1H), 9.07 (d, J = 1.8 Hz, 1H), 8.94 (s, 1H), 8.48 (s, 1H), 7.76 (d, J = 1.8 Hz, 1H), 6.93 (s, 1H), 5.41 (q, 1H), 3.32 (s, 3H), 2.47 (s, 3H), 1.58 (d, J = 6.6 Hz, 3H).; LCMS: 435.20 [M+H]$^+$.

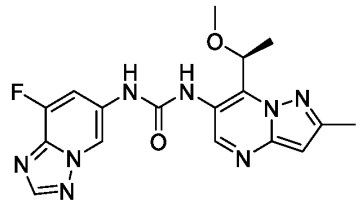
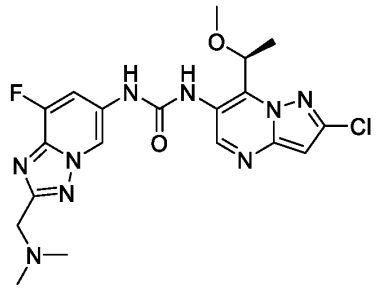
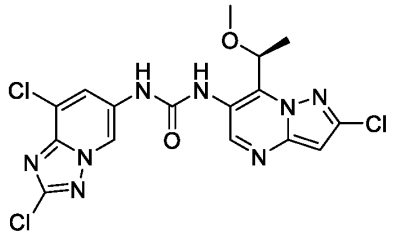
6		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.80 (s, 1H), 9.04-8.95 (m, 2H), 8.48 (s, 1H), 7.75 (d, J = 1.8 Hz, 1H), 6.93 (s, 1H), 5.44-5.27 (q, 1H), 3.32 (s, 3H), 2.20-2.13 (m, 1H), 1.58 (d, J = 6.6 Hz, 3H), 1.08-1.03 (m, 2H), 1.00-0.96 (m, 2H).; LCMS: 461.2 $[M+H]^+$.
7		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.79 (s, 1H), 9.06 (d, J = 1.3 Hz, 1H), 8.93 (s, 1H), 8.47 (s, 1H), 7.77 (d, J = 1.3 Hz, 1H), 6.92 (s, 1H), 5.40 (q, J = 6.7 Hz, 1H), 3.31 (s, 3H), 3.151 m, 1H),1.57 (d, J = 7.0 Hz, 3H), 1.33 (d, J = 7.0 Hz, 6H).; LCMS: 463.20 $[M+H]^+$.
8		^{1}H NMR (400 MHz, Methanol-d_4) δ 9.36 (d, J = 1.8 Hz, 1H), 9.05 (s, 1H), 7.84 (d, J = 1.8 Hz, 1H), 6.69 (s, 1H), 5.56 (q, J = 6.6 Hz, 1H), 3.46 (s, 3H), 1.63 (d, J = 6.4 Hz, 3H).; LCMS: 489.0 $[M+H]^+$.
9		^{1}H NMR (400 MHz, Methanol-d_4) δ 9.05 (d, J = 19.2 Hz, 1H), 7.72-7.60 (m, 1H), 7.45 (dd, J = 11.3, 1.6 Hz, 1H), 6.68 (s, 1H), 5.55 (q, J = 6.8 Hz, 1H), 3.45 (s, 3H), 2.54 (s, 3H), 1.62 (d, J = 6.7 Hz, 3H).; LCMS: 419.1 $[M+H]^+$.

10		^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.49 (s, 1H), 8.28 (s, 1H), 6.90 (s, 1H), 6.64 (s, 1H), 4.15-4.26 (q, J = 6.8 Hz, 1H), 4.01 (s, 3H), 3.28 (s, 3H), 2.60 (s, 3H), 1.56 (d, J = 6.1 Hz, 3H).; LCMS: 431.20 $[M+H]^+$.
11		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92-10.03 (s, 1H), 9.21-9.41 (s, 1H), 8.85-9.03 (s, 1H), 8.41-8.61 (s, 1H), 7.89-8.10 (s, 1H), 6.80-7.03 (s, 1H), 5.32-5.50 (q, 1H), 3.28 (s, 3H), 1.59 (d, J = 6.1 Hz, 3H), 1.23 (s, 3H).; LCMS: 469.20 $[M+H]^+$.
12		^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.84 (s, 1H), 8.56 (s, 1H), 8.08 (s, 1H), 6.63 (s, 1H), 4.68 (s, 1H), 4.02-3.96 (m, 2H), 2.62 (s, 3H), 2.08 (d, J = 36.0 Hz, 2H), 1.25 (s, 2H).; LCMS: 431.20 $[M+H]^+$.
13		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 9.04 (d, J = 40.8 Hz, 1H), 8.53 (s, 1H), 7.62-7.59 (m, 2H), 6.98 (s, 1H), 5.58-5.55 (t, 1H), 5.48-5.43 (q, 1H), 4.68 (d, J = 6.6 Hz, 2H), 3.31 (s, 3H) 1.62 (d, J = 6.6 Hz, 3H).; LCMS: 435.20 $[M+H]^+$.

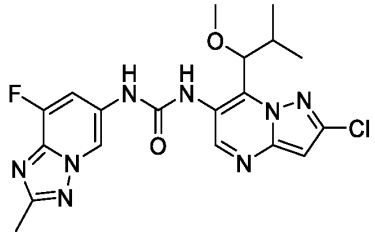
14		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (s, 1H), 8.85-9.07 (s, 1H), 8.19 (s, 1H), 6.89 (s, 1H), 5.41 (q, 1H), 3.28 (s, 3H), 1.59 (d, J = 7.0 Hz, 3H), 1.23 (s, 3H).; LCMS: 426.0 [M+H]$^+$.
15		^{1}H NMR (400 MHz, Methanol-d_4) δ CD3OD) δ 9.01 (s, 1H), 8.48 (s, 1H), 7.53-7.50 (m, 1H), 6.65 (s, 1H), 2.54 (s, 3H), 2.39 (d, J = 8.8 Hz, 1H), 1.63 (d, J = 3.5 Hz, 2H), 1.29-1.25 (m, 2H).; LCMS: 401.0 [M+H]$^+$.
16		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (s, 1H), 8.62 (d, J = 34.2 Hz, 2H), 7.64 (s, 2H), 6.96 (s, 1H), 3.74-3.91 (1H), 2.50 (s, 3H), 1.52 (d, J = 7.0 Hz, 6H).; LCMS: 403.1 [M+H]$^+$.
17		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 9.11 (d, J = 1.6 Hz, 1H), 8.98 (s, 1H), 8.54 (s, 1H), 7.63 (dd, J = 11.7, 1.6 Hz, 1H), 6.97 (s, 1H), 5.45 (q, J = 6.7 Hz, 1H), 4.60 (d, J = 38.0 Hz, 2H), 3.45-3.40 (s, 6H), 1.62 (d, J = 6.7 Hz, 3H).; LCMS: 449.0 [M+H]$^+$.
18		^{1}H NMR (400 MHz, Methanol-d_4) δ 9.56 (d, J = 2.0 Hz, 1H), 9.05 (s, 1H), 8.50 (s, 1H), 8.15 (d, J = 2.0 Hz, 1H), 6.70 (s, 1H), 5.57 (d, J = 6.7 Hz, 1H), 3.47 (s, 3H),

		1.64 (d, J = 6.7 Hz, 3H).; LCMS: 412.1 $[M+H]^+$.
19		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (d, J = 16.8 Hz, 2H), 8.88 (s, 1H), 8.57 (s, 1H), 6.91 (s, 1H), 5.40-5.38 (q, J = 6.7 Hz, 1H), 3.29 (s, 3H), 2.46 (s, 6H), 1.59 (d, J = 6.7 Hz, 3H).; LCMS: 493.0 $[M+H]^+$.
20		^{1}H NMR (400 MHz, Methanol-d_4) δ 9.38 (s, 1H), 9.02 (s, 1H), 8.35 (s, 1H), 7.76 (d, J = 9.8 Hz, 1H), 6.69 (s, 1H), 5.55 (d, J = 6.7 Hz, 1H), 3.45 (s, 3H), 1.64 (d, J = 6.7 Hz, 3H).; LCMS: 387.1 $[M+H]^+$.
21		^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.87 (s, 1H), 8.10 (s, 1H), 7.27 (m, 1H), 6.67 (s, 1H), 5.34 (d, J = 1.6 Hz, 1H), 3.78-3.76 (q, 1H), 3.38 (s, 3 H), 3.14 (s, 3H), 2.61 (s, 3H), 1.44 (d, J = 6.8 Hz, 3H).; LCMS: 462.90 $[M+H]^+$.
22		^{1}H NMR (400 MHz, Methanol-d_4) δ 9.98 (s, 1H), 8.81 (s, 1H), 7.55 (m, 1H), 6.94 (s, 1H), 4.95 (s, 2H), 3.37 (s, 3 H), 2.47 (s, 3H).; LCMS: 405.0 $[M+H]^+$.

23		^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.69 (s, 1H), 9.00 (s, 1H), 8.87 (s, 1H), 8.23 (s, 1H), 7.55 (d, J = 11.8 Hz, 1H), 7.00 (s, 1H), 1.76 (s, 2H), 1.48 (s, 2H).; LCMS: 469.1 [M+H]$^+$.
24		^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.78 (s, 1H), 8.94 (d, J = 42.1 Hz, 2H), 8.43 (s, 1H), 7.54-7.51 (m, 1H), 6.55 (d, J = 5.3 Hz, 1H), 5.32 (t, J = 6.6 Hz, 1H), 3.31 (s, 3H), 2.47 (s, 3H), 1.57 (d, J = 7.0 Hz, 3H).; LCMS: 403.1 [M+H]$^+$.
25		^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.84 (s, 1H), 8.97 (d, J = 26.7 Hz, 2H), 8.46 (s, 1H), 7.53 (d, J = 11.8 Hz, 1H), 6.99 (s, 1H), 5.43 (q, J = 6.6 Hz, 1H), 3.31 (s, 3H), 2.47 (s, 3H), 1.58 (d, J = 6.6 Hz, 3H).; LCMS: 464.0 [M+H]$^+$.
26		^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.78 (s, 1H), 8.99 (d, J = 1.2 Hz, 1H), 8.87 (s, 1H), 8.42 (s, 1H), 7.70 (s, 1H), 7.54-7.51 (m, 2H), 6.52 (s, 1H), 5.37-5.35 (q, 1H), 3.31 (s, 3 H), 2.47 (s, 3H), 1.57 (d, J = 6.4 Hz, 3H).; LCMS: 450.95 [M+H]$^+$.
27		^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.13 (d, J = 3.1 Hz, 2H), 8.52 (s, 1H), 7.59 (d, J = 10.1 Hz, 1H), 7.34 (s, 1H), 5.49 (d, J = 7.0 Hz, 1H), 3.35 (s, 3H), 1.61 (d, J = 6.6

		Hz, 3H).; LCMS: 438.98 [M+H]$^+$.
28		^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.82 (s, 1H), 9.12 (s, 1H), 8.76 (s, 1H), 8.51 (s, 1H), 8.37 (s, 1H), 7.58 (d, J = 11.8 Hz, 1H), 6.56 (s, 1H), 5.4-5.38 (q, 1H), 2.44 (s, 3H), 1.58 (d, J = 6.6 Hz, 3H).; LCMS: 385.0 [M+H]$^+$.
29		^{1}H NMR (400 MHz, Methanol-d$_4$) δ 9.12 (s, 1H), 9.01 (s, 1H), 7.47-7.44 (m, 1H), 6.67 (s, 1H), 5.56-5.51 (q, 1H), 3.78 (s, 2H), 3.46 (s, 3H), 2.36 (s, 6H), 1.61 (d, J = 7.0 Hz, 3H); LCMS: 462.1 [M+H]$^+$.
30		^{1}H NMR (400 MHz, Methanol-d$_4$) δ 9.20 (d, J = 2.0, 1H), 9.02 (s, 1H), 7.75 (d, J = 2.0, 1H), 6.67 (s, 1H), 5.33-5.31 (q, 1H), 3.44 (s, 3H), 1.61 (d, J = 7.0 Hz, 3H); LCMS: 454.8 [M+H]$^+$.

Example-31: 1-(2-chloro-7-(1-methoxy-2-methylpropyl)pyrazolo[1,5-a]pyrimidin-6-yl)-3-(8-fluoro-2-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)urea



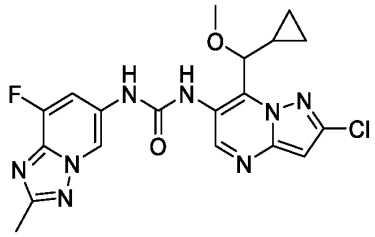
Example-31 was prepared by the similar procedure described for Example-1.

The crude compound was purified by preparative thin layer chromatography (SiO2; 70% EtOAc in hexane) to afford 0.035 g (44.50%) of 1-(2-chloro-7-(1-methoxy-2-methylpropyl)pyrazolo[1,5-a]pyrimidin-6-yl)-3-(8-fluoro-2-methyl-[1,2,4]triazolo[1,5-

a]pyridin-6-yl)urea. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (s, 1H), 9.01 (d, J = 19.6 Hz, 2H), 8.38 (s, 1H), 7.55 (d, J = 10.2 Hz, 1H), 6.97 (s, 1H), 5.10 (s, 1H), 3.38 (s, 3H), 2.51 (s, 3H), 1.27 (m, 1H), 1.11 (d, J = 6.7 Hz, 3H), 0.84 (d, J = 6.7 Hz, 3H).; LCMS: 447.1 [M+H]$^+$.

The racemic compound (0.3g) was separated by SFC. [Column: CHIRALPAK IH (250mm X 21.2mm)5 micron)], Condition: Solvent, A: n-Hexane, B: 0.1% DEA in EtOH, Isocratic: 50(A):50(B), Flow rate: 20 mL/min to give peak-1(Isomer-1; Example-31a) 0.09 g of 1-(2-chloro-7-(1-methoxy-2-methylpropyl)pyrazolo[1,5-a]pyrimidin-6-yl)-3-(8-fluoro-2-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)urea. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (s, 1H), 9.02 (d, J = 20.0 Hz, 2H), 8.38 (s, 1H), 7.55 (d, J = 11.7 Hz, 1H), 6.97 (s, 1H), 5.11 (d, J = 7.0 Hz, 1H), 3.39 (s, 3H), 2.51 (s, 3H), 1.25-1.30 (m, 1H), 1.11 (d, J = 6.7 Hz, 3H), 0.84 (d, J = 6.7 Hz, 3H).; LCMS: 447.0 [M+H]$^+$, and peak-2 (Isomer-2; and Example-31b) 0.09 g of 1-(2-chloro-7-(1-methoxy-2-methylpropyl)pyrazolo[1,5-a]pyrimidin-6-yl)-3-(8-fluoro-2-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)urea. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 (s, 1H), 9.04-8.99 (m, 2H), 7.55 (dd, J = 11.7, 1.6 Hz, 2H), 6.97 (s, 1H), 5.80 (s, 1H), 5.11 (d, J = 7.0 Hz, 1H), 3.38 (s, 3H), 2.52 (s, 3H), 1.22-1.32 (1H), 1.11 (d, J = 6.7 Hz, 3H), 0.84 (d, J = 6.7 Hz, 3H); LCMS: 446.95 [M+H]$^+$.

Example-32: 1-(2-chloro-7-(cyclopropyl(methoxy)methyl)pyrazolo[1,5-a]pyrimidin-6-yl)-3-(8-fluoro-2-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)urea



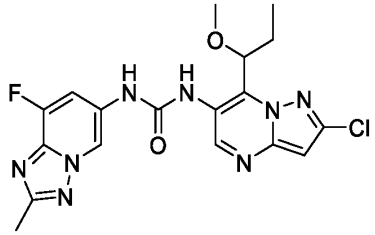
Example-32 was prepared by the similar procedure described for Example-1.

The crude compound was purified by flash column chromatography (SiO2; 70% EtOAc in hexane) to afford 0.180 g (32.58%) of 1-(2-chloro-7-(cyclopropyl(methoxy)methyl)pyrazolo[1,5-a]pyrimidin-6-yl)-3-(8-fluoro-2-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)urea. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 9.04-9.00 (m, 2H), 8.48 (s, 1H), 7.56 (dd, J = 11.7, 1.6 Hz, 1H), 6.98 (s, 1H), 4.81 (d, J = 9.0 Hz, 1H), 3.39 (s, 3H), 2.51 (s, 3H), 1.55-1.52 (m, 1H), 0.71-0.64 (m, 2H), 0.52-0.42 (m, 2H).; LCMS: 445.1 [M+H]$^+$.

The racemic compound (0.15 g) was separated by SFC. [Column: Cellulose-1 (250mm X 20.2mm) 5 micron)], Condition: Solvent, A: n-Hexane, B: EtOH, Flow rate: 18 mL/min to

obtain peak-1 (Isomer-1; Example-32a) 0.02 g of 1-(2-chloro-7-(cyclopropyl(methoxy)methyl)pyrazolo[1,5-a]pyrimidin-6-yl)-3-(8-fluoro-2-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)urea. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (s, 1H), 9.02 (d, J = 19.6 Hz, 2H), 8.49 (s, 1H), 7.57 (d, J = 11.7 Hz, 1H), 6.98 (s, 1H), 4.81 (d, J = 8.6 Hz, 1H), 3.38 (d, J = 6.7 Hz, 3H), 2.52 (s, 3H), 1.47-1.60 (m, 1H), 0.69 (m, 2H), 0.38-0.55 (m, 2H).; LCMS: 445.1 [M+H] $^+$, and peak-2 (Isomer-2; and Example-32b) 0.02 g 1-(2-chloro-7-(cyclopropyl(methoxy)methyl)pyrazolo[1,5-a]pyrimidin-6-yl)-3-(8-fluoro-2-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)urea. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (s, 1H), 9.02 (d, J = 19.6 Hz, 2H), 8.49 (s, 1H), 7.57 (d, J = 11.7 Hz, 1H), 6.98 (s, 1H), 4.81 (d, J = 8.6 Hz, 1H), 3.38 (d, J = 6.7 Hz, 3H), 2.52 (s, 3H), 1.47-1.60 (m, 1H), 0.69 (m, 2H), 0.38-0.55 (m, 2H).; LCMS: 445.1 [M+H] $^+$.

Example-33: 1-(2-chloro-7-(1-methoxypropyl)pyrazolo[1,5-a]pyrimidin-6-yl)-3-(8-fluoro-2-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)urea



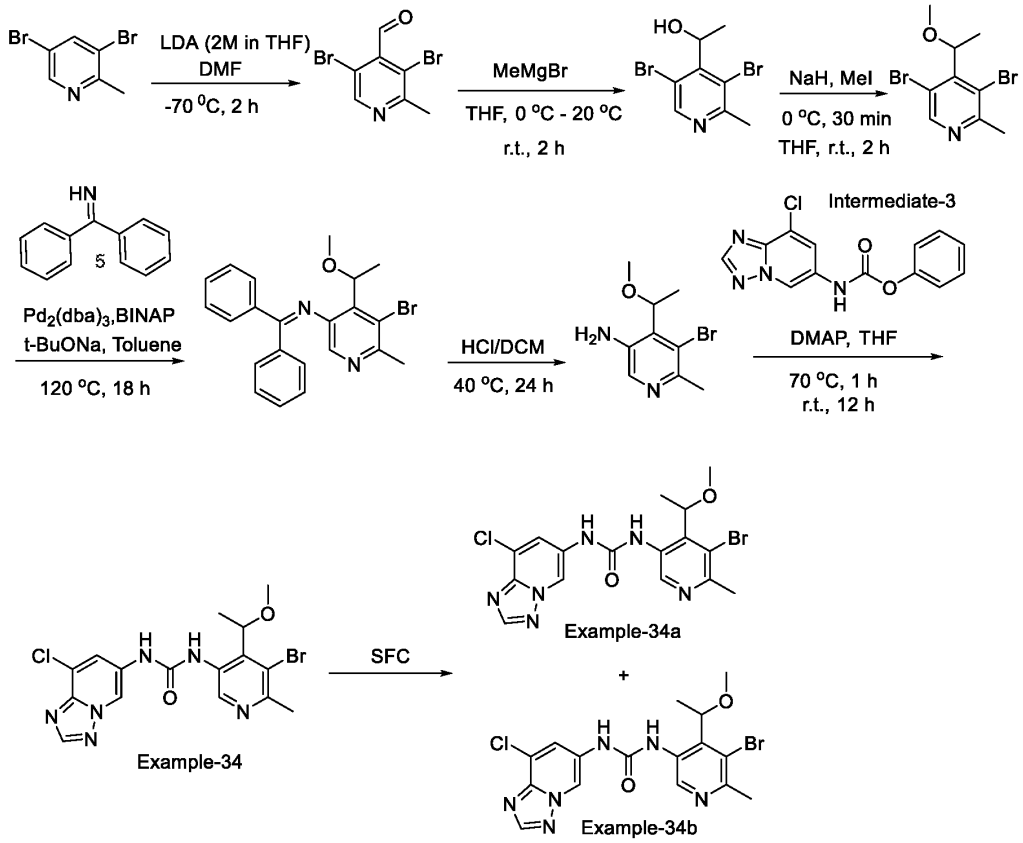
Example-33 was prepared by the similar procedure described for Example-1.

The crude compound was purified by flash column chromatography (SiO_2; 50% EtOAc in hexane) to give 0.15 g (31.16%) of 1-(2-chloro-7-(1-methoxypropyl)pyrazolo[1,5-a]pyrimidin-6-yl)-3-(8-fluoro-2-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)urea ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 9.01 (d, J = 19.2 Hz, 2H), 8.45 (s, 1H), 7.56 (d, J = 11.7 Hz, 1H), 6.96 (s, 1H), 5.31-5.28 (m, 1H), 3.39 (s, 3H), 2.51 (s, 3H), 2.06-1.91 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H); LCMS: 433.1 [M+H] $^+$.

The racemic compound (0.12 g) was separated by SFC. [Column: CHIRALPAK-IG (250mm X 21.2mm) 5-micron, Condition: Solvent, A: n-Hexane, B: EtOH, Time/%B: 0/50, 20/50; Flow rate: 18 mL/min to get peak-1 (Isomer-1; Example-33a) 0.03 g of 1-(2-chloro-7-(1-methoxypropyl)pyrazolo[1,5-a]pyrimidin-6-yl)-3-(8-fluoro-2-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)urea. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.83 (s, 1H), 8.93 (d, J = 19.6 Hz, 2H), 8.37 (s, 1H), 7.48 (d, J = 11.7 Hz, 1H), 6.89 (s, 1H), 5.23-5.20 (m, 1H), 3.30 (s, 3H), 2.43 (s, 3H), 1.95 (d, J = 7.0 Hz, 2H), 0.91 (t, J = 7.2 Hz, 3H).; LCMS: 433.20 [M+H] $^+$, and peak-2 (Isomer-2; and Example-33b) 0.03 g of 1-(2-chloro-7-(1-methoxypropyl)pyrazolo[1,5-

a]pyrimidin-6-yl)-3-(8-fluoro-2-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)urea. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.81-9.94 (1H), 8.93 (d, J = 21.9 Hz, 2H), 8.32-8.47 (1H), 7.42-7.54 (1H), 6.89 (s, 1H), 5.18-5.28 (1H), 3.30 (s, 3H), 2.46-2.43 (s, 3H), 1.76-2.03 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H).; LCMS: 433.1 $[M+H]^+$.

Example-34: 1-(5-bromo-4-(1-methoxyethyl)-6-methylpyridin-3-yl)-3-(8-chloro-[1,2,4]triazolo[1,5-a]pyridin-6-yl)urea



Step-a: Synthesis of 3,5-dibromo-2-methylisonicotinaldehyde

A stirred solution of 3,5-dibromo-2-methylpyridine (3.8 g, 15.14 mmol) in dry THF was cooled to -70 °C, then LDA (2 M in THF) (1.94 g, 18.17 mmol) was added under a nitrogen atmosphere. The reaction was stirred at -70 °C for 1 h. This was followed by addition of DMF (2.5 ml). The reaction mixture was stirred at -70 °C for 1 h. Then the reaction mixture was quenched with saturated NH_4Cl solution at -30 °C to -20 °C, water was added, the mixture was allowed to warm to room temperature, and then it was extracted with EtOAc. The ethyl acetate layer was washed with water, brine, dried over sodium sulfate, filtered and concentrated. The crude compound was purified by flash column chromatography (SiO2; 5-10% EtOAc in

Hexane) to give 1.95 g (46.16%) of 3,5-dibromo-2-methylisonicotinaldehyde. ^{1}H NMR (300 MHz, DMSO-d6) δ 10.08 (s, 1H), 8.75 (s, 1H), 2.62 (s, 3 H).; LCMS: 279.8 $[M+H]^+$.

Step-b: Synthesis of 1-(3,5-dibromo-2-methylpyridin-4-yl)ethan-1-ol

A stirred solution of 3,5-dibromo-2-methylisonicotinaldehyde (1.9 g, 6.81 mmol) in dry THF (30 ml) was cooled to 0 °C, then MeMgBr (3M in DEE) (1.21 g, 10.21 mmol) was added under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 2 h. Then the reaction mixture was quenched with saturated NH_4Cl solution, water was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to give 1.75 g (87.09%) of 1-(3,5-dibromo-2-methylpyridin-4-yl)ethan-1-ol. ^{1}H NMR (300 MHz, DMSO-d6) δ 8.51 (s, 1H), 5.58 (d, J = 3.9 Hz, 1H), 5.39-5.35 (q, 1H), 2.58 (s, 3 H), 1.42 (d, J = 6.6 Hz, 3H).; LCMS: 295.8 $[M+H]^+$.

Step-c: Synthesis of 3,5-dibromo-4-(1-methoxyethyl)-2-methylpyridine

A stirred solution of 1-(3,5-dibromo-2-methylpyridin-4-yl)ethan-1-ol (1.7 g, 5.76 mmol) in dry THF was cooled to 0 °C. Sodium hydride 60% (0.415 g, 17.28 mmol) was added portion wise at 0 °C. The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 30 min and followed by addition of methyl iodide (1.22 g, 8.64 mmol). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 2 h. The reaction mixture was quenched with saturated NH_4Cl solution, water was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, brine, dried over sodium sulfate, filtered and concentrated. The crude compound was purified by flash column chromatography (SiO_2; 5-10% EtOAc in Hexane) to give 1.75 g (98.27%) of 3,5-dibromo-4-(1-methoxyethyl)-2-methylpyridine. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.49 (s, 1H), 5.18-5.16 (q, 1H), 3.16 (s, 3H), 2.64 (s, 3 H), 1.51 (d, J = 6.8 Hz, 3H).; LCMS: 310.0 $[M+H]^+$.

Step-d: Synthesis of N-(5-bromo-4-(1-methoxyethyl)-6-methylpyridin-3-yl)-1,1-diphenylmethanimine

To a stirred solution of 3,5-dibromo-4-(1-methoxyethyl)-2-methylpyridine (1.8 g, 5.82 mmol) in toluene (30 mL) were added diphenylmethanimine (1.16 g, 6.4 mmol), sodium-tertiary butoxide (0.56 g, 5.825 mmol), rac-BINAP (0.54 g, 0.87 mmol) and $Pd_2(dba)_3$ (0.267 g, 0.290 mmol) and then the reaction mixture was degassed with nitrogen for 5 min. The reaction mixture was heated at 120 °C for 18 h. The reaction mixture was cooled and filtered through a Celite® bed. The filtrate was concentrated under reduced pressure to give 2.38 g of

N-(5-bromo-4-(1-methoxyethyl)-6-methylpyridin-3-yl)-1,1-diphenylmethanimine. LCMS: 411.0 $[M+H]^+$.

Step-e: Synthesis of 5-bromo-4-(1-methoxyethyl)-6-methylpyridin-3-amine

To a stirred solution of N-(5-bromo-4-(1-methoxyethyl)-6-methylpyridin-3-yl)-1,1-diphenylmethanimine (3.8 g, 9.28 mmol) in dry DCM, conc. HCl (4 ml) was added, and the reaction mixture was stirred at 40 °C for 24 h. The reaction mixture was cooled to RT, basified with saturated sodium bicarbonate solution and extracted with ethyl acetate. The ethyl acetate layer was dried over sodium sulfate, filtered and concentrated. The crude compound was purified by flash column chromatography (SiO_2; 20-30% EtOAc in Hexane). The pure fraction was concentrated under reduced pressure to give 0.9 g (39.55%) of 5-bromo-4-(1-methoxyethyl)-6-methylpyridin-3-amine. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.79 (s, 1H), 5.38 (bs, 2H), 4.90-4.89 (q, 1H), 3.14 (s, 3H), 2.38 (s, 3 H), 1.33 (d, J = 6.8 Hz, 3H).; LCMS: 245.0 [M+H]

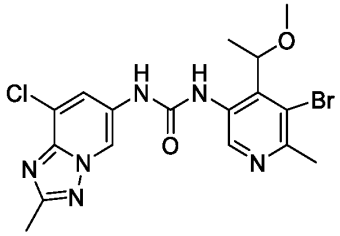
Step-f: Synthesis of 1-(5-bromo-4-(1-methoxyethyl)-6-methylpyridin-3-yl)-3-(8-chloro-[1,2,4]triazolo[1,5-a]pyridin-6-yl)urea

To a stirred solution of 5-bromo-4-(1-methoxyethyl)-6-methylpyridin-3-amine (0.05 g, 0.204 mmol) in 10 mL of dry THF were added DMAP (0.075 g, 0.610 mmol) and phenyl (8-chloro-[1,2,4]triazolo[4,3-a]pyridin-6-yl)carbamate (0.118 g, 0.408 mmol). The reaction mixture was stirred for 1 hour at 70 °C and at RT for 12 hours. The reaction mixture was quenched with water and extracted with EtOAc. The ethyl acetate layer was washed with saturated $KHSO_4$ solution, water, brine solution, dried over anhydrous sodium sulphate and concentrated. The crude compound was purified by flash column chromatography (SiO_2; 5% MeOH in DCM) followed by preparative high-performance liquid chromatography. [Column: LUNA, 250mm x 21.1mm x 5 microns; Condition: A: water, B: ACN, Flow rate: 20 mL/min] to give 0.012 g (13.38%) of 1-(5-bromo-4-(1-methoxyethyl)-6-methylpyridin-3-yl)-3-(8-chloro-[1,2,4]triazolo[1,5-a]pyridin-6-yl)urea. ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.29 (t, J = 1.4 Hz, 1H), 9.06 (d, J = 1.2 Hz, 1H), 8.40 (s, 1H), 7.75 (d, J = 2.0 Hz, 1H), 5.19 (s, 1H), 3.39 (s, 3H), 2.64 (s, 3H), 1.51 (d, J = 7.0 Hz, 3H); LCMS: 440.9 $[M+H]^+$.

Racemic compound (0.009 g) was separated by SFC. [Column: CELLULOSE-4 (250mm X 21.2), 5µm. Condition: Solvent, A: n-Hexane, B: Ethanol. Isocratic: Time/%B 0/40, 20/40, Flow rate: 20 mL/min to obtain peak-1(Isomer-1; Example-34a) 0.0025 g (25.0%) of 1-(5-bromo-4-(1-methoxyethyl)-6-methylpyridin-3-yl)-3-(8-chloro-[1,2,4]triazolo[1,5-a]pyridin-6-yl)urea. ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.29 (d, J = 2.0 Hz, 1H), 9.07 (s, 1H), 8.40 (s, 1H), 7.76 (d, J = 2.0 Hz, 1H), 5.21 (q, J = 6.8 Hz, 1H), 3.40 (s, 3H), 2.65 (s, 3H), 1.52

(d, J = 6.7 Hz, 3H); LCMS: 441.10 $[M+H]^+$, and peak-2 (Isomer-2; Example-34b) 0.0025 g (25.0%) of 1-(5-bromo-4-(1-methoxyethyl)-6-methylpyridin-3-yl)-3-(8-chloro-[1,2,4]triazolo[1,5-a]pyridin-6-yl)urea. ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.28 (d, J = 2.0 Hz, 1H), 9.06 (s, 1H), 8.39 (s, 1H), 7.75 (d, J = 2.0 Hz, 1H), 5.20 (t, J = 6.7 Hz, 1H), 3.39 (s, 3H), 2.64 (s, 3H), 1.51 (d, J = 7.0 Hz, 3H).; LCMS: 440.9 $[M+H]^+$.

Example-35: 1-(5-bromo-4-(1-methoxyethyl)-6-methylpyridin-3-yl)-3-(8-chloro-2-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)urea



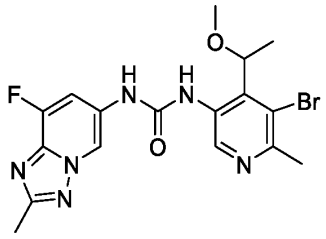
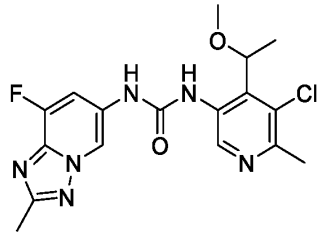
Example-35 was prepared by the similar procedure described for Example-34.

The crude compound was purified by flash column chromatography over silica gel. (SiO_2; 50-60% EtOAc in hexane) to get 0.04 g (21.61%) of 1-(5-bromo-4-(1-methoxyethyl)-6-methylpyridin-3-yl)-3-(8-chloro-2-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)urea. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (s, 1H), 9.07-8.97 (m, 2H), 8.71 (d, J = 9.9 Hz, 1H), 7.73 (d, J = 1.8 Hz, 1H), 5.06 (q, J = 6.8 Hz, 1H), 3.33 (s, 3H), 2.58 (s, 3H), 2.47 (s, 3H), 1.44 (d, J = 6.8 Hz, 3H).; LCMS: 454.85 $[M+H]^+$.

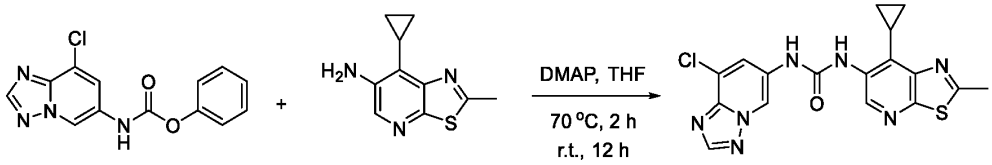
Racemic compound (0.03 g) was separated by SFC. [Column: Chiral pack (250mm X 20mm), 5µm. Condition: Solvent, %A: Ethanol, %B: n-Hexane. Isocratic: Time/B: 0.1/40 and 10/40; Flow rate: 18 mL/min. to get peak-1(Isomer-1; Example-35a) 0.01 g (33.39%) of 1-(5-bromo-4-(1-methoxyethyl)-6-methylpyridin-3-yl)-3-(8-chloro-2-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)urea. (400 MHz, Methanol-d_4) δ 9.17 (d, J = 2.0 Hz, 1H), 9.06 (s, 1H), 7.69 (d, J = 2.0 Hz, 1H), 5.19 (t, J = 6.8 Hz, 1H), 3.39 (s, 3H), 2.64 (s, 3H), 2.54 (s, 3H), 1.51 (d, J = 7.0 Hz, 3H).; LCMS: 455.10 $[M+H]^+$, and peak-2 (Isomer-2; Example-35b) 0.01 g (33.39%) of 1-(5-bromo-4-(1-methoxyethyl)-6-methylpyridin-3-yl)-3-(8-chloro-2-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)urea. ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.17 (d, J = 1.6 Hz, 1H), 9.06 (s, 1H), 7.70 (d, J = 2.0 Hz, 1H), 5.20 (q, J = 6.8 Hz, 1H), 3.39 (s, 3H), 2.64 (s, 3H), 2.54 (s, 3H), 1.51 (d, J = 6.7 Hz, 3H).; LCMS: 455.10 $[M+H]^+$.

The below compounds were prepared by the analogous procedure described in Example-34 with appropriate variations in reactants, quantities of reagents, solvents and

reaction conditions. The physiochemical characteristics of the compounds are summarized in the below table.

Example	Structure	Analytical data
36		^{1}H NMR (400 MHz, Methanol-d_4) δ 9.08-9.06 (m, 2H), 7.45 (dd, J = 11.3, 1.6 Hz, 1H), 5.20 (q, J = 6.8 Hz, 1H), 3.39 (s, 3H), 2.65 (s, 3H), 2.54 (s, 3H), 1.51 (d, J = 6.7 Hz, 3H); LCMS: 437.1 $[M+H]^+$.
37		(400 MHz, Methanol-d_4) δ 9.05 (d, J = 11.3 Hz, 2H), 7.44 (d, J = 9.9 Hz, 1H), 5.19 (t, J = 6.8 Hz, 1H), 3.37 (s, 3H), 2.54 (d, J = 16.7 Hz, 6H), 1.50 (d, J = 6.8 Hz, 3H).; LCMS: 393.20 $[M+H]^+$.

Example-38: 1-(8-chloro-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-(7-cyclopropyl-2-methylthiazolo[5,4-b]pyridin-6-yl)urea

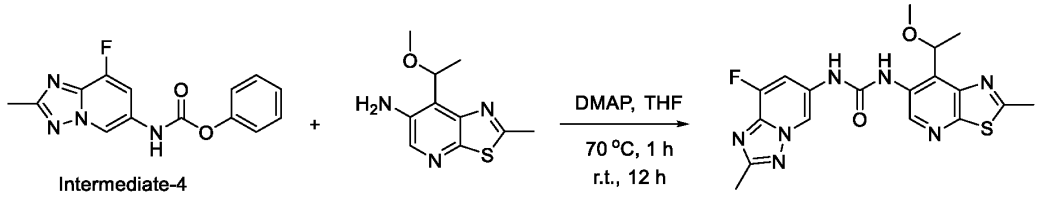


Intermediate-3

To a stirred solution of 7-cyclopropyl-2-methylthiazolo[5,4-b]pyridin-6-amine ((Synthesized by using Ref WO2018020474) 0.15 g, 0.731 mmol) in 2 mL of dry THF were added DMAP (0.134 g, 1.101 mmol) and phenyl (8-chloro-[1,2,4]triazolo[4,3-a]pyridin-6-yl)carbamate (0.423 g, 1.468 mmol). The reaction mixture was stirred for 2 hours at 70 °C and then stirred at room temperature for 12 h. The reaction mixture was quenched with water and extracted with EtOAc. The ethyl acetate layer was washed with water, brine solution, dried over anhydrous sodium sulphate and concentrated. The crude compound was purified by flash column chromatography (SiO2; 40-50% EtOAc in Hexane). The pure fraction was concentrated under reduced pressure to get 0.035 g (11.97%) of 1-(8-chloro-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-(7-cyclopropyl-2-methylthiazolo[5,4-b]pyridin-6-

yl)urea. ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.22-9.27 (1H), 8.64 (s, 1H), 8.41 (s, 1H), 7.78-7.82 (1H), 2.82 (s, 3H), 1.55-1.61 (m, J= 2.4 Hz, 1H), 1.17-1.34 (m, J = 6.8 Hz, 4H).; LCMS: 400.20 $[M+H]^+$.

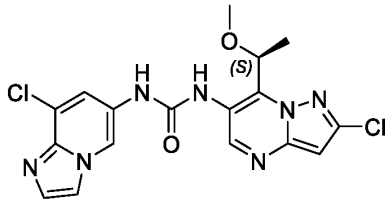
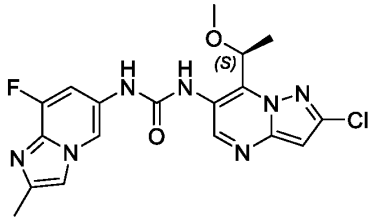
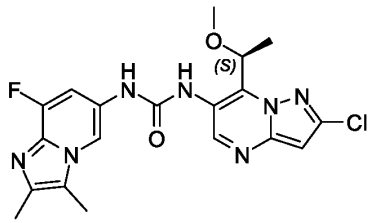
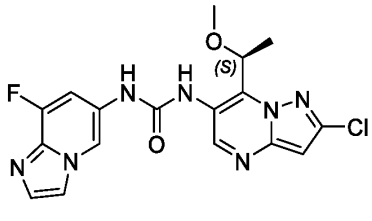
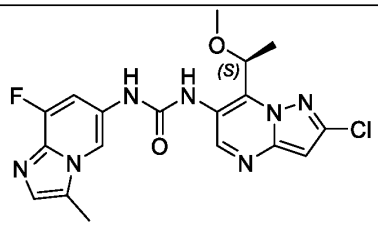
Example-39: 1-(8-fluoro-2-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-(7-(1-methoxyethyl)-2-methylthiazolo[5,4-b]pyridin-6-yl)urea

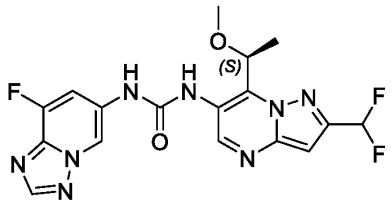
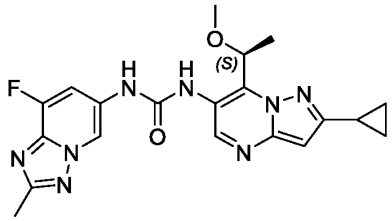
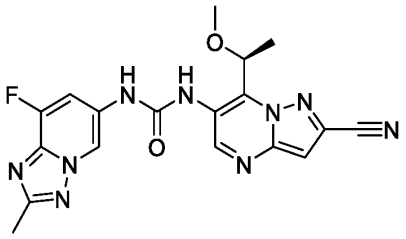
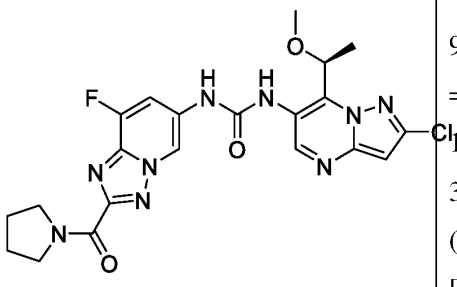


To a stirred solution of 7-(1-methoxyethyl)-2-methylthiazolo[5,4-b]pyridin-6-amine ((prepared according to the procedure described in WO2018020474); 0.05 g, 0.244 mmol) in 8 mL of dry THF were added DMAP (0.041 g, 0.33 mmol) and phenyl (8-fluoro-2-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)carbamate (0.096 g, 0.336 mmol). The reaction mixture was stirred for 1 hour at 70 °C and then stirred at room temperature for 12 h. The reaction mixture was quenched with water and extracted with EtOAc. The ethyl acetate layer was washed with water, brine solution then dried over anhydrous sodium sulphate and concentrated. The crude compound was purified by flash column chromatography (SiO_2; 40-50% EtOAc in Hexane) to get 0.02 g (21.49%) of 1-(8-fluoro-2-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-(7-(1-methoxyethyl)-2-methylthiazolo[5,4-b]pyridin-6-yl)urea. ^{1}H NMR (300 MHz, Methanol-d_4) δ 9.18 (s, 1H), 9.09 (s, 1H), 7.50-7.45 (t, 1H), 5.60-5.57 (q, 1H), 3.40 (s, 3 H), 2.84 (s, 3H), 2.54 (s, 3H), 1.58 (d, J = 6.6 Hz, 3H).; LCMS: 416.1 $[M+H]^+$.

The compounds given in the following table were prepared by the procedure similar to the one described in Example-I with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. The physiochemical characteristics of the compounds are summarized in the table below.

Example	Structure	Analytical data

40		1H-NMR (400 MHz, DMSO) δ 9.65 (s, 1H), 8.95 (d, J = 2.4 Hz, 2H), 8.42 (s, 1H), 8.12 (s, 1H), 7.58 (s, 1H), 7.39 (s, 1H), 6.92 (s, 1H), 5.42 (q, 1H), 3.31 (s, 3H), 1.58 (d, J = 6.6 Hz, 3H).; LCMS: 421.9 $[M+H]^+$.
41		^{1}H NMR (400 MHz, Methanol-d_4) δ 9.00 (d, J = 13.3 Hz, 1H), 7.78 (d, J = 2.0 Hz, 1H), 7.67 (dd, J = 12.3, 2.2 Hz, 2H), 6.67 (d, J = 5.9 Hz, 1H), 5.527 (q, 1H), 3.45-3.39 (m, 3H), 2.16 (s, 3H), 1.61 (d, J = 6.7 Hz, 3H).; LCMS: 418.1 $[M+H]^+$.
42		^{1}H NMR (400 MHz, Methanol-d_4) δ 9.03 (s, 1H), 8.84 (s, 1H), 7.61 (d, J = 11.3 Hz, 1H), 6.70 (s, 1H), 5.57 (q, 1H), 3.46 (s, 3H), 2.52 (d, J = 5.5 Hz, 6H), 1.63 (d, J = 7.0 Hz, 3H).; LCMS: 432.1 $[M+H]^+$.
43		^{1}H NMR (400 MHz, Methanol-d_4) δ 9.00 (s, 1H), 8.82 (s, 1H), 7.92 (s, 1H), 7.55 (s, 1H), 7.06 (d, J = 13.6 Hz, 1H), 6.66 (s, 1H), 5.54 (q, 1H), 3.43 (s, 3H), 1.60 (d, J = 7.0 Hz, 3H).; LCMS: 404.1 $[M+H]^+$.
44		^{1}H NMR (400 MHz, Methanol-d_4) δ 9.04 (s, 1H), 8.57 (s, 1H), 7.39 (s, 1H), 7.07 (d, J = 11.8 Hz, 1H), 6.69 (s, 1H), 5.56 (q, 1H), 3.47 (s, 3H),

		2.51 (s, 3H), 1.63 (d, J = 6.6 Hz, 3H).; LCMS: 418.20 $[M+H]^+$.
45		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 9.07 (d, J = 45.6 Hz, 2H), 8.54 (d, J = 15.8 Hz, 2H), 7.59 (d, J = 11.4 Hz, 1H), 7.27 (s, 1H), 7.06 (s, 1H), 5.49 (q, 1H), 3.34 (s, 3H), 1.60 (d, J = 6.6 Hz, 3H).; LCMS: 420.95 $[M+H]^+$.
46		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.75 (d, J = 4.4 Hz, 1H), 8.99 (d, J = 3.9 Hz, 1H), 8.72 (d, J = 2.2 Hz, 1H), 8.34 (d, J = 3.1 Hz, 1H), 7.54-7.50 (m, 1H), 6.43 (d, J = 2.2 Hz, 1H), 5.49 (q, 1H), 3.31 (s, 3H), 2.46 (d, J = 3.9 Hz, 3H), 1.57 (d, J = 7.0 Hz, 3H), 1.23 (m, 1H), 1.03 (m, 2H), 0.85 (m, 2H).; LCMS: 425.2 $[M+H]^+$.
47		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (s, 1H), 9.18 (s, 1H), 9.01 (s, 1H), 8.64 (s, 1H), 7.60-7.52 (m, 2H), 5.48 (q, 1H), 3.35 (s, 3H), 2.48 (s, 3H), 1.59 (d, J = 6.6 Hz, 3H).; LCMS: 409.95 $[M+H]^+$.
48		^{1}H NMR (400 MHz, Methanol-d_4) δ 9.21 (s, 1H), 9.02 (s, 1H), 7.51 (d, J = 11.0 Hz, 1H), 6.67 (s, 1H), 5.54 (q, 1H), 3.94 (m, 2H), 3.67 (m, 2H), 3.44 (s, 3H), 2.02-1.96 (t, 4H), 1.61 (d, J = 6.6 Hz, 3H).; LCMS: 502.1 $[M+H]^+$.

Example P1: Biochemical Assay

The potency of compounds to inhibit MALT-1 (Isoform1) enzyme was tested in a Fluorescent assay using recombinant MALT-1 (Isoform1, aa-840) generated in-house. The assay buffer was 50 mM HEPES (pH 7.5), 100 mM NaCl, 10 mM DTT, 1 mM EDTA, 0.9 M sodium citrate, 0.01% CHAPS. 1.5 nM of MALT-1 enzyme was incubated with various concentrations of test compounds (1 µM) (1% DMSO) in the presence of buffer for 30 minutes at 30°C. The protease reaction was initiated by adding 50 µM of AC-LRSR-MAC (Peptide International, USA) substrate and incubated for 240 min. After 240 min incubation, fluorescence emission of the samples at 460 nm was measured at an excitation of 355 nm. The percent inhibition was calculated using the following formula: (Control OD − (Sample OD/Control OD)) × 100. IC_{50} values were determined by fitting the dose-response data to sigmoidal curve fitting equation using Graph pad prism software V8.

Selected compounds of the present invention were screened in the above-mentioned assay procedure for the determination of IC_{50} values and the results are summarized into groups +++, ++ and + in the table below. Herein, the group "+++" encompasses the compounds having IC_{50} values lower than 0.05 µM, the group "++" encompasses the compounds having IC_{50} values between 0.051 µM and 0.25 µM (both inclusive) and the group "+" encompasses the compounds having IC_{50} values higher than 0.25 µM. 'ND' refers to Not determined.

Example	IC_{50} (µM)	Percent Inhibition (@ 1µM)
1	+++	94
2	+++	97
3	+++	96
4	++	94
5	+++	98
6	+++	97
7	+++	96
8	+++	94
9	+++	92
10	+	38
11	+++	98
12	++	81
13	++	84
14	+++	99
15	++	79
16	+++	90
17	+++	82

Example	IC_{50} (µM)	Percent Inhibition (@ 1µM)
18	+++	98
19	+	17
20	+	16
21	+	96
22	+	62
23	+	98
24	++	80
25	+++	95
26	+	71
27	++	87
28	+	84
29	++	83
30	+++	96
31	+++	100
31a	+++	100
31b	+++	99

Example	IC_{50} (μM)	Percent Inhibition (@ 1μM)
32	+++	100
32a	++	96
32b	+++	99
33	+++	98
33a	+++	99
33b	++	96
34	+	71
34a	++	79
34b	ND	33
35	+	72
35a	++	88
35b	+	8

Example	IC_{50} (μM)	Percent Inhibition (@ 1μM)
36	+	69
37	+	48
38	+	62
39	+	77
40	++	96
41	+	69
42	++	79
43	++	86
44	++	90
45	++	78
46	+++	40
47	+++	54
48	++	86

Incorporation by Reference

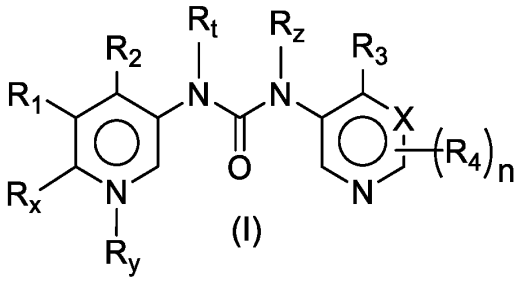
All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent were specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

Equivalents

While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification and the claims below. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents and the specification, along with such variations.

We claim:

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof; wherein,

X represents N or C;

R_x and R_y combine together with the atoms to which they are attached to form a fused 5-membered heteroaryl substituted with 1 or 2 occurrence(s) of R_6;

R_t and R_z independently represents hydrogen or alkyl;

R_1 is hydrogen, halogen, cyano, hydroxy, amino, alkoxy, alkyl or haloalkyl;

R_2 is hydrogen, halogen, alkyl or haloalkyl;

R_3 is aryl, cycloalkyl, heterocyclyl or a group represented by a formula $-CHR_aR_b$, wherein the aryl, cycloalkyl and heterocyclyl are optionally substituted with 1, 2 or 3 substituent(s) independently selected from halogen, hydroxy, haloalkyl and alkyl;

R_a and R_b independently represent hydrogen, alkyl, alkoxy, alkoxy-alkyl, haloalkyl or cycloalkyl;

R_4 at each occurrence is independently hydrogen, halogen, alkyl, alkoxy, haloalkyl, haloalkoxy or cycloalkyl; or any two adjacent R_4 groups combine together with the atoms to which they are attached to form a fused 5-membered heteroaryl substituted with 1 or 2 occurrence(s) of R_5;

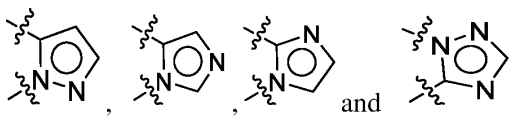
R_5 at each occurrence is independently hydrogen, alkyl, halogen, haloalkyl, cyano, alkoxy, haloalkoxy, amino, aryl, cycloalkyl, heterocycloalkyl or heteroaryl;

R_6 at each occurrence is independently hydrogen, halogen, hydroxy, cyano, alkoxy, alkyl or cycloalkyl, wherein the alkyl is optionally substituted with 1 to 3 substituent(s) independently selected from hydroxy, oxo, halogen, alkylamino, alkoxy and heterocycloalkyl; and

n is 1, 2 or 3.

2. The compound of claim 1, wherein X represents N.

3. The compound of any one of claims 1 to 2, wherein R_x and R_y combine together with the atoms to which they are attached to form a fused 5-membered heteroaryl substituted with 1 or 2 occurrence(s) of R_6.

4. The compound of claim 3, wherein the fused 5-membered heteroaryl is selected from  ; wherein ~~~ represents points of fusion.

5. The compound of any one of claims 1 to 4, wherein R_1 represents hydrogen, halogen, cyano, alkoxy or haloalkyl.

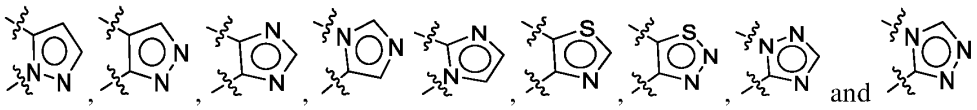
6. The compound of any one of claims 1 to 5, wherein R_2 represents hydrogen or alkyl.

7. The compound of any one of claims 1 to 6, wherein

R_3 is 3- to 10- membered cycloalkyl, 3- to 10-membered heterocycloalkyl or a group represented by the formula $-CHR_aR_b$, wherein the cycloalkyl and heterocycloalkyl are optionally substituted with 1 or 2 substituent(s) independently selected from halogen, haloalkyl and alkyl; and

R_a and R_b independently represent hydrogen, alkyl, alkoxy, alkoxy-alkyl or 3- to 10- membered cycloalkyl.

8. The compound of any one of claims 1 to 7, wherein R_4 at each occurrence is independently hydrogen, halogen or alkyl; or any two adjacent R_4 groups combine together with the atoms to which they are attached to form a fused 5-membered heteroaryl substituted with 1 or 2 occurrence(s) of R_5.

9. The compound of claim 8, wherein the fused 5-membered heteroaryl is selected from  ; wherein ~~~ represents points of fusion.

10. The compound of any one of claims 1 to 9, wherein R_5 at each occurrence is independently hydrogen, alkyl, halogen, haloalkyl, haloalkoxy, cyano or cycloalkyl.

11. The compound of any one of claims 1 to 10, wherein R_6 at each occurrence is independently hydrogen, halogen, alkyl, alkyl-OH, alkyl-N(alkyl)$_2$, alkoxy-alkyl, haloalkyl, -C(=O)-(5- to 6-membered heterocycloalkyl) or 3- to 10-membered cycloalkyl.

12. The compound of any one of claims 1 to 11, wherein

X represents N or C;

R_1 represents hydrogen, halogen, cyano, alkoxy or haloalkyl;

R_2 represents hydrogen or alkyl;

R_x and R_y combine together with the atoms to which they are attached to form a fused 5-membered heteroaryl substituted with 1 or 2 occurrence(s) of R_6;

R_3 is 3- to 10-membered cycloalkyl, 3- to 10-membered heterocycloalkyl or a group represented by the formula -CH$R_a$$R_b$, wherein the cycloalkyl and heterocycloalkyl are optionally substituted with haloalkyl;

R_a and R_b independently represent hydrogen, alkyl, alkoxy, alkoxy-alkyl or 3- to 10- membered cycloalkyl;

R_4 at each occurrence is independently hydrogen, halogen or alkyl; or any two adjacent R_4 groups combine together with the atoms to which they are attached to form a fused 5-membered heteroaryl substituted with 1 or 2 occurrence(s) of R_5;

R_5 at each occurrence is independently hydrogen, alkyl, halogen, haloalkyl, haloalkoxy, cyano or cycloalkyl;

R_6 at each occurrence is independently hydrogen, halogen, alkyl, alkyl-OH, alkyl-N(alkyl)$_2$, alkoxy-alkyl, haloalkyl, -C(=O)-(5- to 6-membered heterocycloalkyl) or 3- to 10- membered cycloalkyl; and

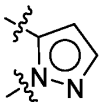
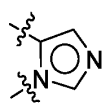
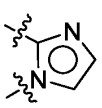
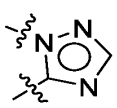
n is 1 or 2.

13. The compound of any one of claims 1 to 12, wherein,

X represents N or C;

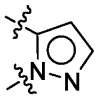
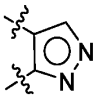
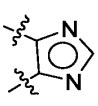
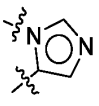
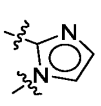
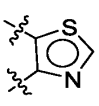
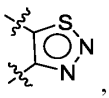
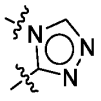
R_1 represents hydrogen, halogen, cyano, alkoxy or halo(C_1-C_6)alkyl;

R_2 represents hydrogen or (C_1-C_6)alkyl;

R_x and R_y combine together with the atoms to which they are attached to form a fused 5-membered heteroaryl selected from  ,  ,  and  ; wherein ~~~ represents points of fusion and each ring is substituted with 1 or 2 occurrence(s) of R_6;

R_3 is 3- to 10-membered cycloalkyl, 3- to 10-membered heterocycloalkyl or a group represented by the formula $-CHR_aR_b$, wherein the cycloalkyl and heterocycloalkyl are optionally substituted with halo(C_1-C_6)alkyl;

R_a and R_b independently represent hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy-(C_1-C_6)alkyl or 3- to 10- membered cycloalkyl;

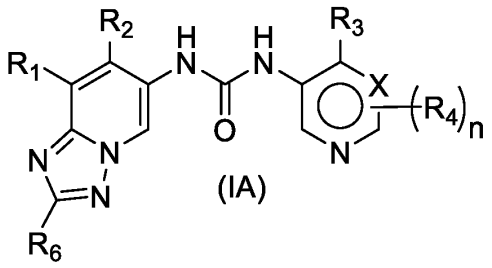
R_4 at each occurrence is independently hydrogen, halogen or (C_1-C_6)alkyl; or any two adjacent R_4 groups combine together with the atoms to which they are attached to form a fused 5-membered heteroaryl selected from  ,  ,  ,  ,  ,  ,  ,  and  ; wherein ~~~ represents points of fusion and each ring is optionally substituted with 1 or 2 occurrence(s) of R_5;

R_5 at each occurrence is independently hydrogen, (C_1-C_6)alkyl, halogen, halo(C_1-C_6)alkyl, halo (C_1-C_6)alkoxy, cyano or 3- to 10-membered cycloalkyl;

R_6 at each occurrence is independently hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkyl-OH, (C_1-C_6)alkyl-N(C_1-C_6)alkyl)$_2$, (C_1-C_6)alkoxy-(C_1-C_6)alkyl-, halo(C_1-C_6)alkyl, -C(=O)-(5- to 6-membered heterocycloalkyl) or 3- to 10-membered cycloalkyl; and

n is 1 or 2.

14. The compound of claim 1, represented by compound of formula (IA)



15. The compound of claim 14, wherein R_1 represents hydrogen, halogen, cyano, (C_1-C_6)alkoxy or halo(C_1-C_6)alkyl.

16. The compound of any one of claims 14 to 15, wherein R_2 represents hydrogen or (C_1-C_6)alkyl.

17. The compound of any one of claims 14 to 16, wherein R_6 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkyl-OH, (C_1-C_6)alkyl-N[(C_1-C_6)alkyl]$_2$, (C_1-C_6)alkoxy-(C_1-C_6)alkyl-, halo(C_1-C_6)alkyl, -C(=O)-(5- to 6-membered heterocycloalkyl) or 3- to 10-membered cycloalkyl.

18. The compound of any one of claims 14 to 17, wherein R_4 at each occurrence is independently hydrogen, halogen or (C_1-C_6)alkyl; or any two adjacent R_4 groups combine together with the atoms to which they are attached to form a fused 5-membered heteroaryl substituted with 1 or 2 occurrence(s) of R_5.

19. The compound of anyone of claims 14 to 18, wherein

X represents N or C;

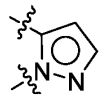
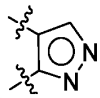
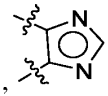
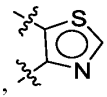
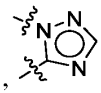
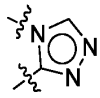
R_1 represents hydrogen, halogen, cyano, alkoxy or halo(C_1-C_6)alkyl;

R_2 represents hydrogen or (C_1-C_6)alkyl;

R_3 is 3- to 10-membered cycloalkyl, 3- to 10-membered heterocycloalkyl or a group represented by the formula -CHR_aR_b, wherein the cycloalkyl and heterocycloalkyl are optionally substituted with halo(C_1-C_6)alkyl;

R_a and R_b independently represent hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy-(C_1-C_6)alkyl or 3- to 10- membered cycloalkyl;

R_4 at each occurrence is independently hydrogen, halogen or (C_1-C_6)alkyl; or any two adjacent R_4 groups combine together with the atoms to which they are attached

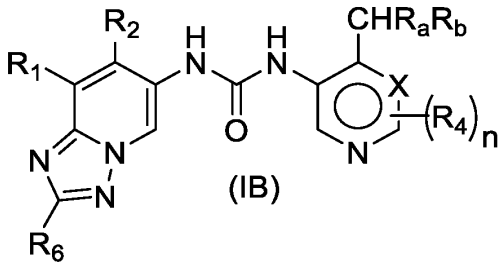
to form a fused 5-membered heteroaryl selected from  ,  ,  ,  ,  ,  ,  ,  ,  ; wherein represents points of fusion and each ring is optionally substituted with 1 or 2 occurrence(s) of R_5;

R_5 at each occurrence is independently hydrogen, $(C_1\text{-}C_6)$alkyl, halogen, halo$(C_1\text{-}C_6)$alkyl, halo $(C_1\text{-}C_6)$alkoxy, cyano or 3- to 10-membered cycloalkyl;

R_6 is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-OH, $(C_1\text{-}C_6)$alkyl-N($(C_1\text{-}C_6)$alkyl)$_2$, $(C_1\text{-}C_6)$alkoxy-$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, -C(=O)-(5- to 6-membered heterocycloalkyl) or 3- to 10- membered cycloalkyl; and

n is 1 or 2.

20. The compound of claim 1, represented by compound of formula (IB)



(IB)

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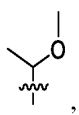
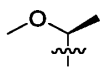
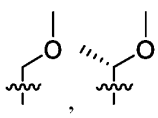
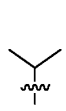
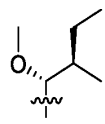
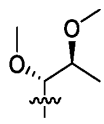
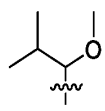
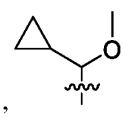
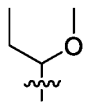
21. The compound of claim 20, wherein

R_a and R_b independently represent hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxy-$(C_1\text{-}C_6)$alkyl or 3- to 10-membered cycloalkyl.

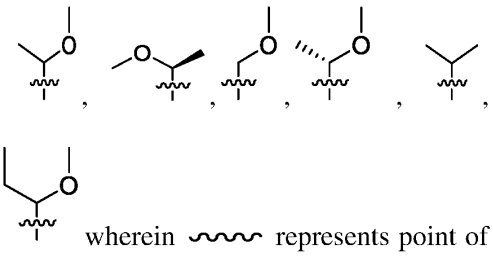
22. The compound of any one of claims 20 to 21, wherein the formula -CHR_aR_b represents  ,  ,  ,  ,  ,  ,  ,  , or  ; wherein represents point of attachment.

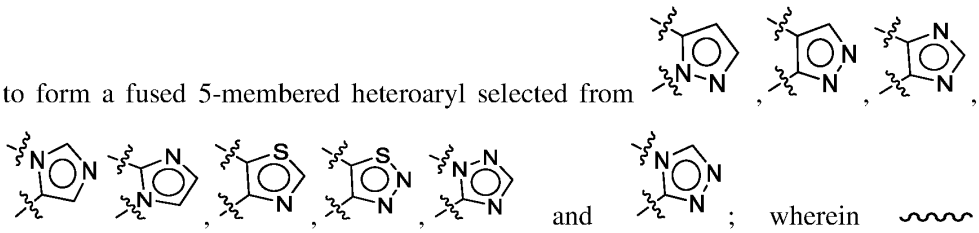
23. The compound of any one of claims 20 to 22, wherein

R_1 represents hydrogen, halogen, cyano, (C_1-C_6)alkoxy or halo(C_1-C_6)alkyl;

R_2 represents hydrogen or (C_1-C_6)alkyl;

R_a and R_b independently represent hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy-(C_1-C_6)alkyl or 3- to 10- membered cycloalkyl;

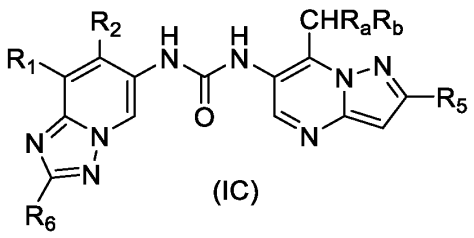
the formula -CHR_aR_b represents  , wherein ~~~ represents point of attachment;

R_4 at each occurrence is independently hydrogen, halogen or (C_1-C_6)alkyl; or any two adjacent R_4 groups combine together with the atoms to which they are attached to form a fused 5-membered heteroaryl selected from  ; wherein ~~~ represents points of fusion; and each ring is optionally substituted with 1 or 2 occurrence(s) of R_5;

R_5 at each occurrence is independently hydrogen, (C_1-C_6)alkyl, halogen, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, cyano or 3- to 10-membered cycloalkyl; and

R_6 is hydrogen, halogen, (C_1-C_6)alkyl, (C_1-C_6)alkyl-OH, (C_1-C_6)alkyl-N((C_1-C_6)alkyl)$_2$, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, -C(=O)-(5- to 6-membered heterocycloalkyl) or 3- to 10-membered cycloalkyl.

24. The compound of claim 1, represented by compound of formula (IC)



(IC)

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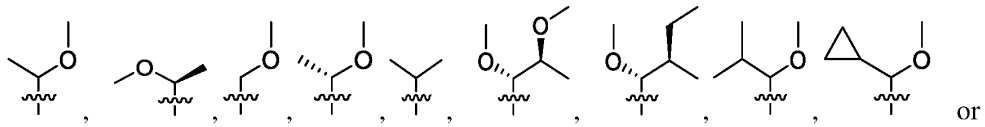
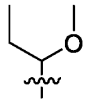
25. The compound of claim 24, wherein R_a represents $(C_1\text{-}C_6)$alkoxy.

26. The compound of any one of claims 24 to 25, wherein R_b represents hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy-$(C_1\text{-}C_6)$alkyl or 3- to 10- membered cycloalkyl.

27. The compound of anyone of claims 24 to 26, wherein the formula -CHR_aR_b represents  or  ; wherein ~~~ represents point of attachment.

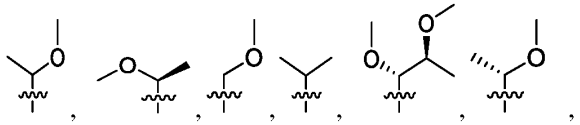
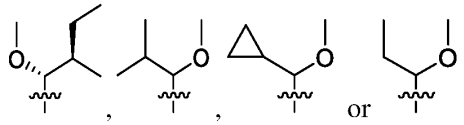
28. The compound of anyone of claims 24 to 27, wherein

R_1 represents hydrogen, halogen, cyano, $(C_1\text{-}C_6)$alkoxy or halo$(C_1\text{-}C_6)$alkyl;

R_2 represents hydrogen or $(C_1\text{-}C_6)$alkyl;

R_a represents $(C_1\text{-}C_6)$alkoxy;

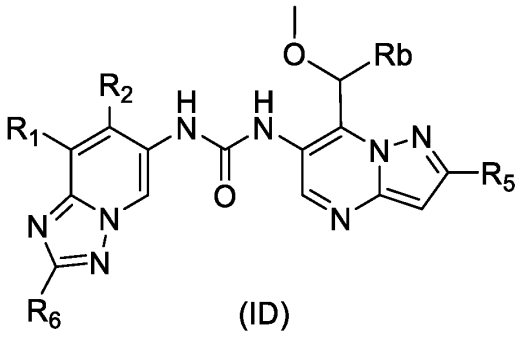
R_b represents hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy-$(C_1\text{-}C_6)$alkyl or 3- to 10-membered cycloalkyl;

the formula -CHR_aR_b represents   or ; wherein ~~~ represents point of attachment;

R_5 is hydrogen, $(C_1\text{-}C_6)$alkyl, halogen, halo$(C_1\text{-}C_6)$alkyl,halo$(C_1\text{-}C_6)$alkoxy, cyano or 3- to 10-membered cycloalkyl; and

R_6 is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-OH, $(C_1\text{-}C_6)$alkyl-N($(C_1\text{-}C_6)$alkyl)$_2$, $(C_1\text{-}C_6)$alkoxy-$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, -C(=O)-(5- to 6-membered heterocycloalkyl) or 3- to 10- membered cycloalkyl.

29. The compound of claim 1, represented by compound of formula (ID)



(ID)

30. The compound of claim 29, wherein R_b represents hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy-$(C_1\text{-}C_6)$alkyl or 3- to 10- membered cycloalkyl.

31. The compound of anyone of claims 29 to 30, wherein

R_1 represents hydrogen, halogen, cyano, $(C_1\text{-}C_6)$alkoxy or halo$(C_1\text{-}C_6)$alkyl;

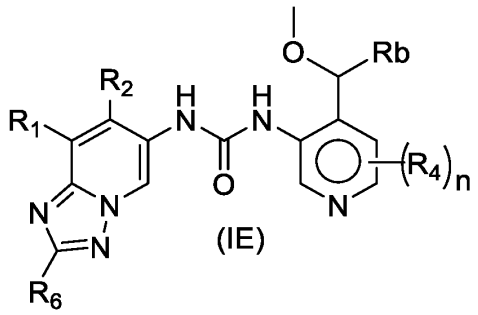
R_2 represents hydrogen or $(C_1\text{-}C_6)$alkyl;

R_b represents hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy-$(C_1\text{-}C_6)$alkyl or 3- to 10-membered cycloalkyl;

R_5 is $(C_1\text{-}C_6)$alkyl, halogen, halo$(C_1\text{-}C_6)$alkyl, cyano or 3- to 10-membered cycloalkyl; and

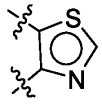
R_6 is hydrogen, halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-OH, $(C_1\text{-}C_6)$alkyl-N($(C_1\text{-}C_6)$alkyl)$_2$, $(C_1\text{-}C_6)$alkoxy-$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, -C(=O)-(5- to 6-membered heterocycloalkyl) or 3- to 10- membered cycloalkyl.

32. The compound of claim 1, represented by compound of formula (IE)



(IE)

33. The compound of claim 32, wherein R_4 is hydrogen, halogen or $(C_1\text{-}C_6)$alkyl; or any two adjacent R_4 groups combine together with the atoms to which they are attached to

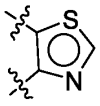
form  optionally substituted with 1 or 2 occurrence(s) of halogen, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, cyano or 3- to 10-membered cycloalkyl, wherein ~~~ represents points of fusion.

34. The compound of anyone of claims 32 to 33, wherein

R_1 represents hydrogen or halogen;

R_2 represents hydrogen;

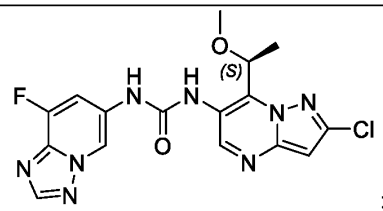
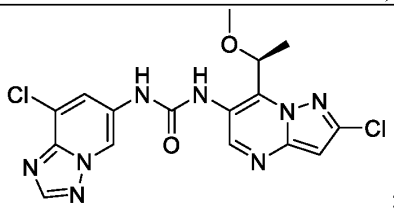
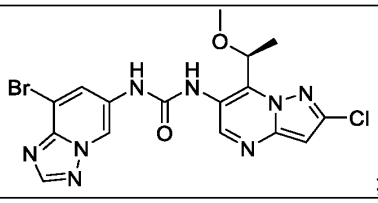
R_b represents (C_1-C_6)alkyl;

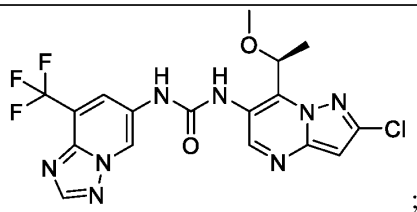
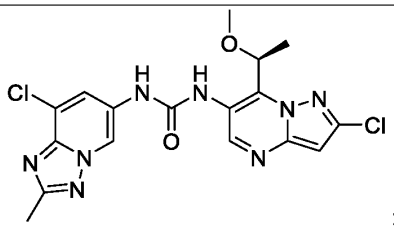
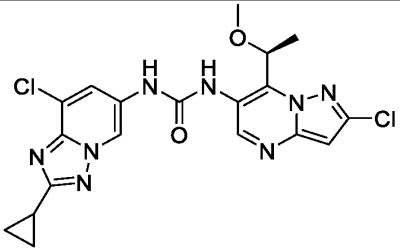
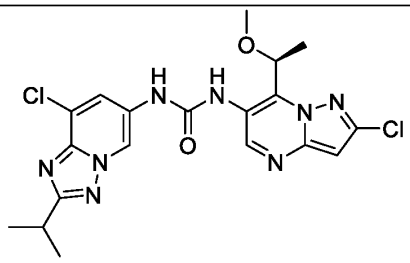
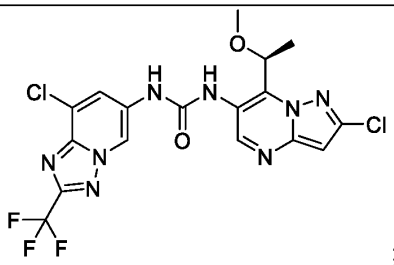
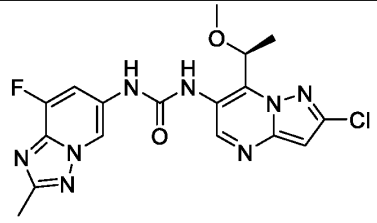
R_4 at each occurrence is independently hydrogen, halogen or (C_1-C_6)alkyl; or any two adjacent R_4 groups combine together with the atoms to which they are attached to form  optionally substituted with 1 or 2 occurrence(s) of halogen or (C_1-C_6)alkyl, wherein ~~~ represents points of fusion;

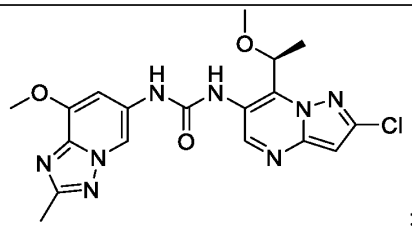
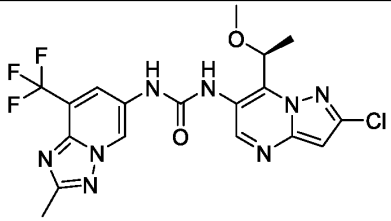
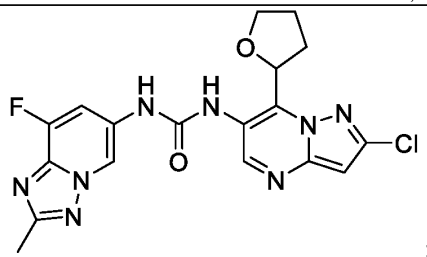
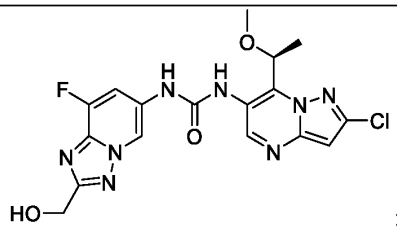
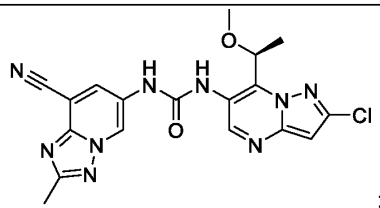
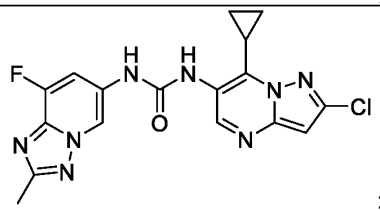
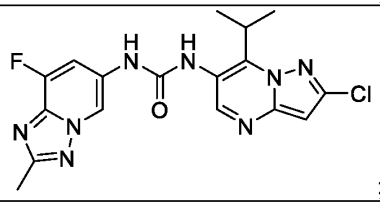
R_6 is hydrogen or (C_1-C_6)alkyl; and

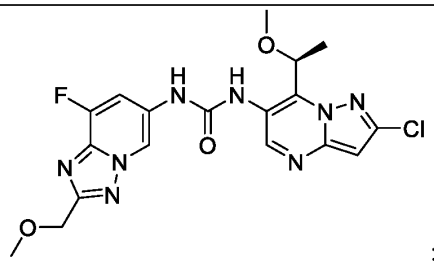
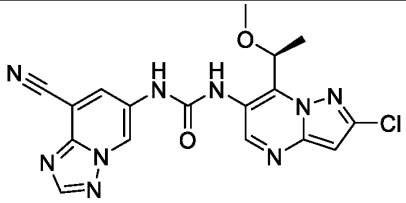
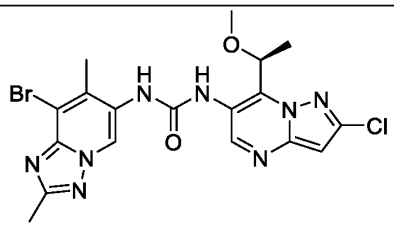
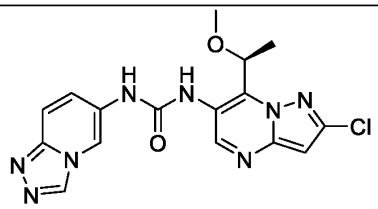
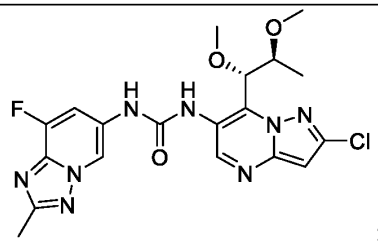
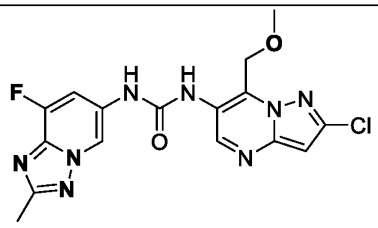
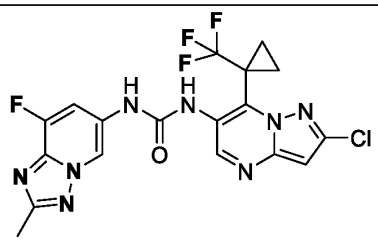
n is 1 or 2.

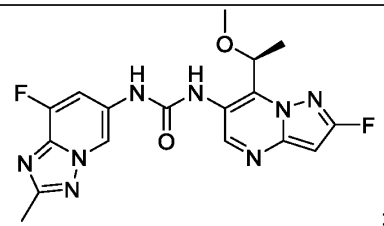
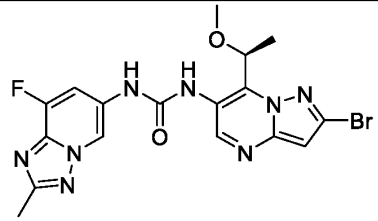
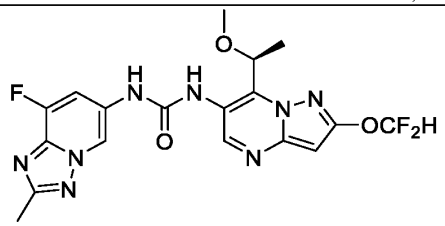
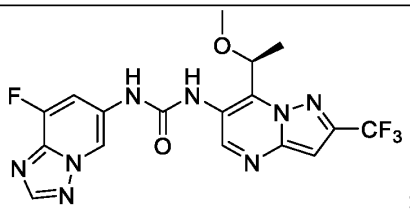
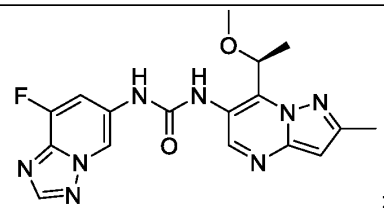
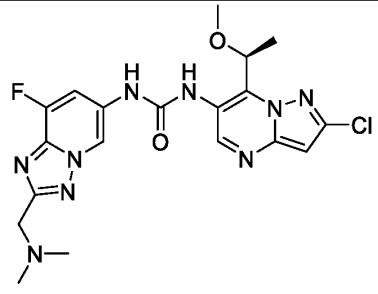
35. The compound of any one of claims 1 to 34, is selected from:

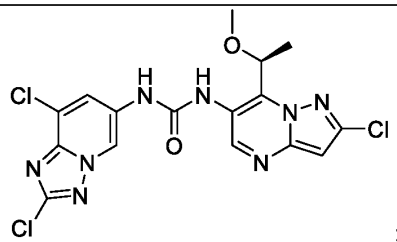
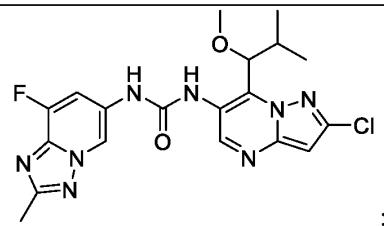
Example	Structure
1	 ;
2	 ;
3	 ;

4	 ;
5	 ;
6	 ;
7	 ;
8	 ;
9	 ;

10	 ;
11	 ;
12	 ;
13	 ;
14	 ;
15	 ;
16	 ;

17	 ;
18	 ;
19	 ;
20	 ;
21	 ;
22	 ;
23	 ;

24	 ;
25	 ;
26	 ;
27	 ;
28	 ;
29	 ;

30	 ;
31	 ;
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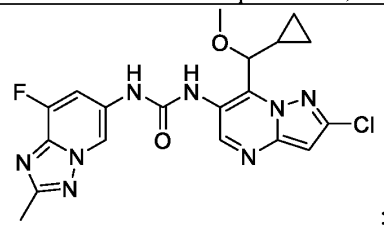
32	 ;
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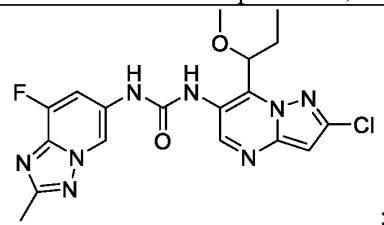
33	 ;
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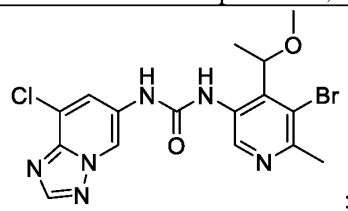
34	 ;
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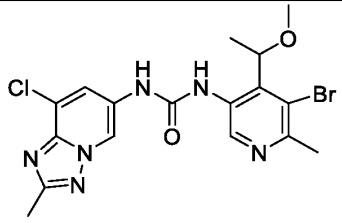
35	 ;

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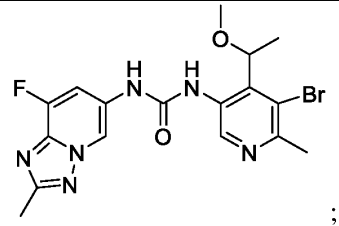
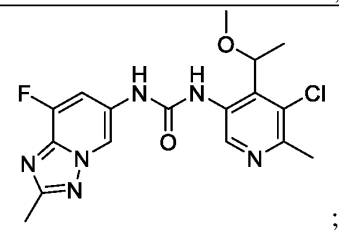
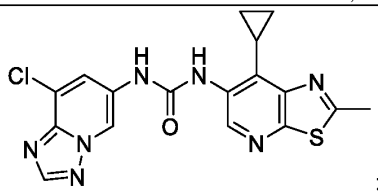
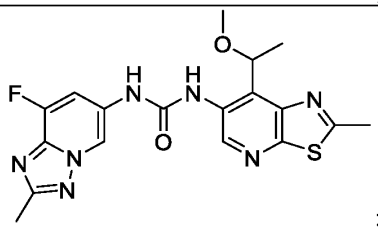
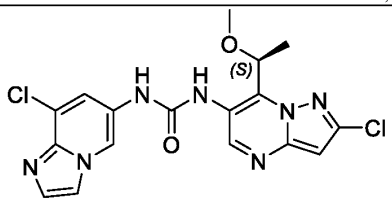
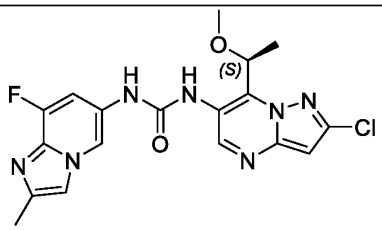
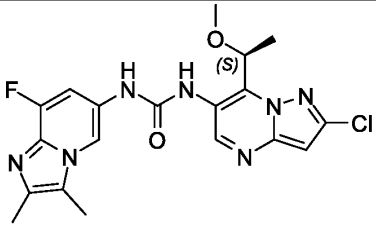
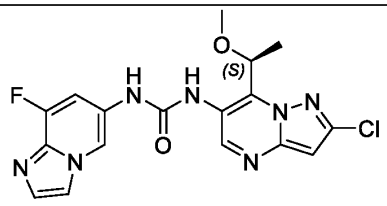
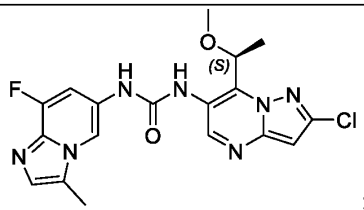
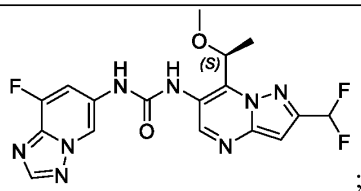
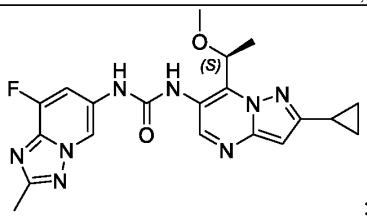
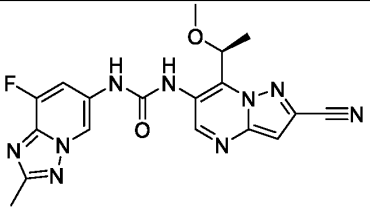
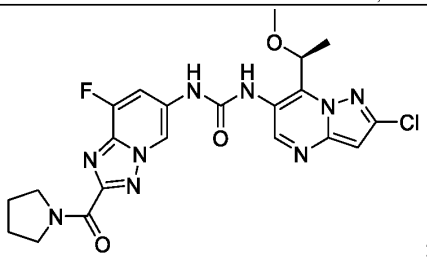
36	 ;
37	 ;
38	 ;
39	 ;
40	 ;
41	 ;
42	 ;

43	 ;
44	 ;
45	 ;
46	 ;
47	 ; and
48	 ;

or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

36. A pharmaceutical composition comprising the compound of any one of claims 1 to 35 or a pharmaceutically acceptable salt or stereoisomer or a tautomer thereof and a pharmaceutically acceptable carrier or excipient.

37. The pharmaceutical composition according to claim 36, for use as a medicament.

38. The pharmaceutical composition according to claim 36, for use in treating or preventing of a disease or disorder mediated by MALT-1.

39. The pharmaceutical composition for use according to claim 38, wherein the disease or disorder is selected from bladder cancer, colon cancer, hepatocellular cancer, Small Cell lung cancer, Non-Small Cell lung cancer, B-cell lymphoma (Diffuse large B-cell lymphoma), mantle cell lymphoma, follicular lymphoma and mucosa-associated lymphoid tissue lymphoma, rheumatoid arthritis, psoriatic arthritis, psoriasis, ulcerative colitis, Crohn's disease, systemic lupus erythematosus, asthma and chronic obstructive pulmonary disease.

40. A compound of any one of claims 1 to 35 or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, for use as a medicament.

41. A method of treating a disease or disorder mediated by the inhibition of MALT-1 in a subject comprising administering to the subject, in need thereof, a therapeutically effective amount of a compound of formula (I) according to any one of claims 1 to 35.

42. The method of claim 41, wherein the disease or disorder mediated by MALT-1 is cancer.

43. The method of claim 41 or 42, wherein the disease or disorder mediated by MALT-1 is selected from bladder cancer, colon cancer, hepatocellular cancer, Small Cell lung cancer, Non-Small Cell lung cancer, B-cell lymphoma (Diffuse large B-cell lymphoma), mantle cell lymphoma, follicular lymphoma and mucosa-associated lymphoid tissue lymphoma, rheumatoid arthritis, psoriatic arthritis, psoriasis, ulcerative colitis, Crohn's disease, systemic lupus erythematosus, asthma and chronic obstructive pulmonary disease.

44. Use of a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, in the manufacture of a medicament for treating or preventing a disease or disorder mediated by the inhibition of MALT-1.

45. The use according to claim 44, where in disease or disorder mediated by the inhibition of MALT-1 is selected from bladder cancer, colon cancer, hepatocellular cancer, Small Cell lung cancer, Non-Small Cell lung cancer, B-cell lymphoma (Diffuse large B-cell lymphoma), mantle cell lymphoma, follicular lymphoma and mucosa-associated lymphoid tissue lymphoma, rheumatoid arthritis, psoriatic arthritis, psoriasis, ulcerative colitis, Crohn's disease, systemic lupus erythematosus, asthma and chronic obstructive pulmonary disease.

46. A compound of any one of claims 1 to 35, for use in treating a disease or disorder mediated by MALT-1.

47. The compound for use according to claim 46, wherein disease or disorder mediated by the inhibition of MALT-1 is selected from bladder cancer, colon cancer, hepatocellular cancer, Small Cell lung cancer, Non-Small Cell lung cancer, B-cell lymphoma (Diffuse large B-cell lymphoma), mantle cell lymphoma, follicular lymphoma and mucosa-associated lymphoid tissue lymphoma, rheumatoid arthritis, psoriatic arthritis, psoriasis, ulcerative colitis, Crohn's disease, systemic lupus erythematosus, asthma and chronic obstructive pulmonary disease.