Small molecule tool compound inhibitors of MALT1 protease have demonstrated efficacy in preclinical models of ABC-DLBCL. Interestingly, covalent catalytic site and allosteric inhibitors of MALT1 protease function have been described, suggesting that inhibitors of this protease may be useful as pharmaceutical agents.

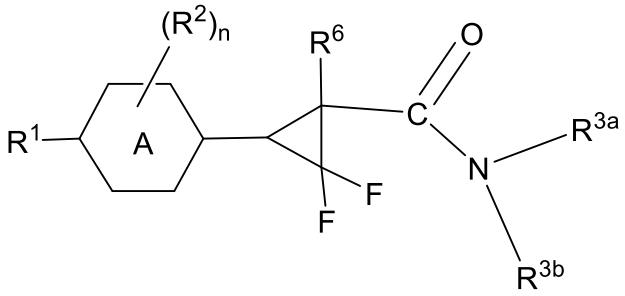
The chromosomal translocation creating the API2-MALT1 fusion oncoprotein is the most common mutation identified in MALT (mucosa-associated lymphoid tissue) lymphoma. API2-MALT1 is a potent activator of the NF_KB pathway. API2-MALT1 mimics ligand-bound TNF receptor, promotes TRAF2-dependent ubiquitination of RIP1 which acts as a scaffold for activating canonical NF_KB signaling. Furthermore, API2-MALT1 has been shown to cleave and generate a stable, constitutively active fragment of NF_KB-inducing kinase (NIK) thereby activating the non-canonical NF_KB pathway.

In addition to lymphomas, MALT1 has been shown to play a critical role in innate and adaptive immunity. MALT1 protease inhibitor can attenuate disease onset and progression of mouse experimental allergic encephalomyelitis, a mouse model of multiple sclerosis. Mice expressing catalytically inactive MALT1 mutant showed loss of marginal zone B cells and B1 B cells and general immune deficiency characterized as decreased T and B cell activation and proliferation. However, those mice also developed spontaneous multi-organ autoimmune inflammation at the age of 9 to 10 weeks. It is still poorly understood why MALT1 protease dead knock-in mice show a break of tolerance while conventional MALT1 KO mice do not. One hypothesis suggests the unbalanced immune homeostasis in MALT1 protease dead knock-in mice may be caused by incomplete deficiency in T and B cell but severe deficiency of immunoregulatory cells. Similarly, MALT deficiency in humans has been associated with combined immunodeficiency disorder. Given the difference between genetic mutation and pharmacological inhibition, a phenotype of MALT1 protease dead knock-in mice might not resemble that of patients treated with MALT1 protease inhibitors. A reduction of immunosuppressive T cells by MALT1 protease inhibition may be beneficial to cancer patients by potentially increasing antitumor immunity.

Thus, MALT1 inhibitors of the present invention may provide a therapeutic benefit to patients suffering from cancer and/or immunological diseases.

SUMMARY

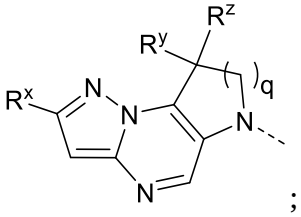
The present disclosure, in one aspect, is directed to a compound of Formula (I)



(I)

or a tautomer or a stereoisomeric form thereof, wherein

R^1 represents



;

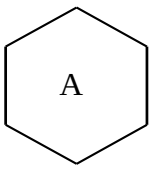
q is 1 or 2;

R^x represents hydrogen; C_{1-4}alkyl; halo; or C_{1-4}alkyl substituted with one, two or three halo substituents;

R^y represents hydrogen; C_{1-4}alkyl; C_{3-6}cycloalkyl; or C_{1-4}alkyl substituted with one, two or three halo substituents;

R^z represents C_{1-4}alkyl; C_{3-6}cycloalkyl; or C_{1-4}alkyl substituted with one, two or three halo substituents;

or R^y and R^z taken together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

ring  represents phenyl or pyridyl;

R^2 represents halo;

n is 0, 1 or 2;

R^{3a} represents hydrogen or C_{1-4}alkyl;

R^{3b} represents hydrogen; C_{1-4}alkyl; C_{3-6}cycloalkyl; adamantyl; C_{6-10}carbobicyclic; Het^1;

C_{3-6}cycloalkyl substituted with one, two, three or four substituents each independently selected from the group consisting of oxo, halo, cyano, -OH, $-OR^7$, $-S(=O)_2-R^7$, $-S(=O)_2-NR^{4a}R^{4b}$, $-NR^{4a}R^{4b}$, $-S(=O)(=NH)-R^7$, $-N=S(=O)-(C_{1-4}alkyl)_2$, $-NH-(C=O)-R^7$, $-C(=O)-NR^{4a}R^{4b}$, $-S(=O)(=NH)-NR^{4a}R^{4b}$, $-P(=O)-R^{4c}R^{4d}$, $-O-C_{1-4}alkyl-C(=O)-NR^{4a}R^{4b}$, $-S(=O)(=NH)-C_{1-4}alkyl-O-R^7$, $-NH-S(=O)_2-R^7$, Het^{3a}, Het^{3b}, and C_{1-4}alkyl optionally substituted with one, two or three substituents each

$S(=O)_2$, or S(=O)(=NH);

R^{4a} and R^{4b} each independently represent hydrogen, C_{1-4}alkyl, C_{3-6}cycloalkyl, or C_{1-4}alkyl-O-C_{1-4}alkyl;

R^{4c} and R^{4d} each independently represent C_{1-4}alkyl or -O-C_{1-4}alkyl;

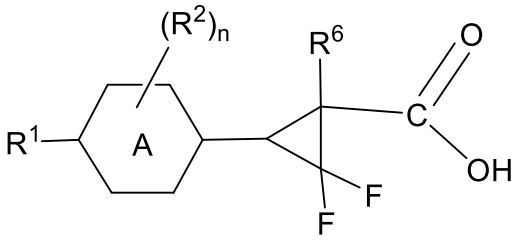
R^6 represents C_{1-4}alkyl; or C_{1-4}alkyl substituted with one -OH;

R^7 represents C_{1-4}alkyl or C_{3-6}cycloalkyl, each optionally substituted with one, two or three halo substituents;

p1 and p2 each independently are 1, 2 or 3;

or a pharmaceutically acceptable salt thereof.

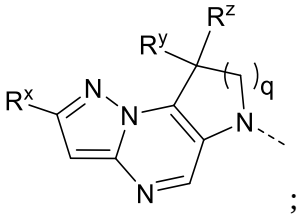
The present disclosure is also directed to active intermediates of Formula (A)



(A)

and the tautomers and the stereoisomeric forms thereof, wherein

R^1 represents



;

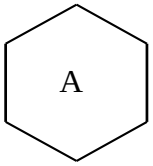
q is 1 or 2;

R^x represents hydrogen; C_{1-4}alkyl; halo; or C_{1-4}alkyl substituted with one, two or three halo substituents;

R^y represents C_{1-4}alkyl; C_{3-6}cycloalkyl; or C_{1-4}alkyl substituted with one, two or three halo substituents;

R^z represents C_{1-4}alkyl; C_{3-6}cycloalkyl; or C_{1-4}alkyl substituted with one, two or three halo substituents;

or R^y and R^z taken together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;



ring A represents phenyl or pyridyl;

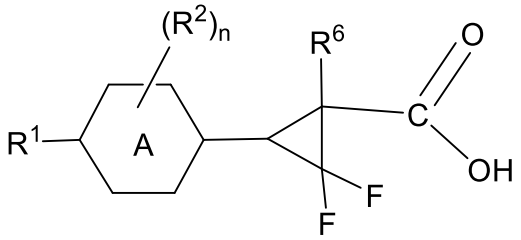
R^2 represents halo;

n is 0, 1 or 2;

R^6 represents C_{1-4}alkyl; or C_{1-4}alkyl substituted with one -OH;

and the pharmaceutically acceptable salts thereof.

In another aspect, there is provided a compound of Formula (A)

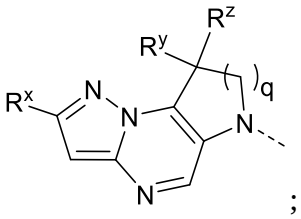


(A)

Formula (A)

or a tautomer or a stereoisomeric form thereof, wherein

R^1 represents



;

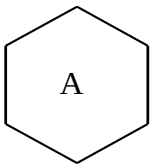
q is 1 or 2;

R^x represents hydrogen; C_{1-4}alkyl; halo; or C_{1-4}alkyl substituted with one, two or three halo substituents;

R^y represents C_{1-4}alkyl; C_{3-6}cycloalkyl; or C_{1-4}alkyl substituted with one, two or three halo substituents;

R^z represents C_{1-4}alkyl; C_{3-6}cycloalkyl; or C_{1-4}alkyl substituted with one, two or three halo substituents;

or R^y and R^z taken together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;



ring A represents phenyl or pyridyl;

R^2 represents halo;
n is 0, 1 or 2;
R^6 represents C_{1-4}alkyl; or C_{1-4}alkyl substituted with one -OH;

or a pharmaceutically acceptable salt thereof.

All references to "compound(s) of Formula (I)" and "intermediates of Formula (A)", in the context of this disclosure, might also refer to a solvate or a pharmaceutically acceptable salt form thereof, even if not explicitly referred to, and are included in the scope of the present disclosure. It will be clear this also applies to subgroups of Formula (I) and Formula (A).

The compounds of Formula (I) and intermediates of Formula (A) may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the disclosure embrace both solvated and unsolvated forms.

As used herein, bonds shown only as solid lines and not as solid wedged or hashed wedged bonds, hashed or bold bonds, or otherwise indicated as having a particular configuration (e.g. by a stereodescriptor such as *R*, *S, 'R or S', 'S or R',* trans, cis) around one or more atoms, contemplate each possible stereoisomer (stereoisomeric form), or mixture of two or more stereoisomers. Where the stereochemistry of any particular chiral atom is not specified in the structures shown herein, then all possible stereoisomers are contemplated and included as the compounds of the disclosure, either as a pure stereoisomer or as a mixture of two or more stereoisomers.

Hereinbefore and hereinafter, the term "compound(s) of Formula (I)" is also meant to include the tautomers and the stereoisomeric forms (stereoisomers; for example enantiomers and diastereomers) thereof, even if not explicitly referred to. However, where stereochemistry, as mentioned in the previous paragraph, is specified by bonds which are shown as solid wedged or hashed wedged bonds, hashed or bold bonds, or are otherwise indicated as having a particular configuration (e.g. *R*, *S, 'R or S', 'S or R',* trans, cis), then that stereoisomer is so specified and defined. It will be clear this also applies to subgroups of Formula (I). It will be clear this also applies to corresponding intermediates of Formula (A).

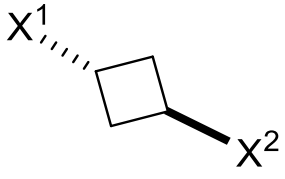
In the context of this disclosure it should be understood that bonds shown as solid lines but indicated with a stereodescriptor, mean that such a stereocenter is specified and defined

according to the stereodescriptor.

In the context of this disclosure it should be understood that bonds shown as solid lines but indicated with *'R or S'* or *'S or R'*, are used to indicate that such a stereocenter is chirally pure but with unknown configuration (pure stereoisomers and enantiomerically pure, but absolute stereochemistry undetermined on stereocenter indicated with *'R or S'* or *'S or R'*).

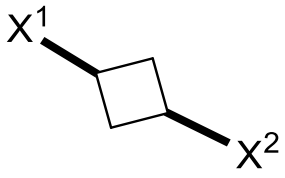
Substituents on bivalent cyclic saturated (for example a cyclopropyl moiety) or partially saturated radicals may have either the cis- or trans-configuration. Terms like 'trans A' or 'trans B' mean that one particular trans form was obtained but that the absolute stereochemistry was undetermined.

It will be clear for a skilled person that a hashed bond and a bold bond on a 1,3-disubstituted cyclobutyl moiety as shown below:



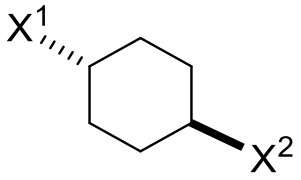
, whereby X^1 and X^2 represent substituents,
indicate that the substituents on the cyclobutyl moiety have trans-configuration.

It will be clear for a skilled person that the bold bonds on a 1,3-disubstituted cyclobutyl moiety as shown below:



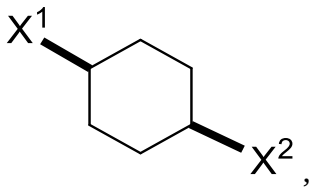
, whereby X^1 and X^2 represent substituents,
indicate that the substituents on the cyclobutyl moiety have cis-configuration.

It will be clear for a skilled person that a hashed bond and a bold bond on a 1,4-disubstituted cyclohexyl moiety as shown below:



, whereby X^1 and X^2 represent substituents,
indicate that the substituents on the cyclohexyl moiety have trans-configuration.

It will be clear for a skilled person that the bold bonds on a 1,4-disubstituted cyclohexyl moiety as shown below:



, whereby X^1 and X^2 represent substituents, indicate that the substituents on the cyclohexyl moiety have cis-configuration.

Atropisomers (or atropoisomers) are stereoisomers which have a particular spatial configuration, resulting from a restricted rotation about a single bond, due to large steric hindrance. All atropisomeric forms of the compounds of Formula (I) are intended to be included within the scope of the present disclosure.

If a compound contains a double bond, the substituents may be in the *E* or the *Z* configuration.

Therefore, the disclosure and the term "compound(s) of Formula (I)" is also meant to include enantiomers, atropisomers, diastereomers, racemates, *E* isomers, *Z* isomers, cis isomers, trans isomers and mixtures thereof, whenever chemically possible. It will be clear this also applies to intermediates of Formula (A).

The meaning of all those terms, i.e. enantiomers, atropisomers, diastereomers, racemates, *E* isomers, *Z* isomers, cis isomers, trans isomers and mixtures thereof are known to the skilled person. The configuration is specified in line with standard priority rules according to the Cahn-Ingold-Prelog system.

The term "compound(s) of the (present) invention (or disclosure)" or "compound(s) according to the (present) invention (or disclosure)" as used herein, is meant to include the compounds of Formula (I) including tautomers and stereoisomeric forms, the pharmaceutically acceptable salt forms, and the solvates thereof.

The present disclosure also provides a pharmaceutical composition comprising, consisting of and/or consisting essentially of a pharmaceutically acceptable carrier, a pharmaceutically acceptable excipient, and/or a pharmaceutically acceptable diluent and a compound of Formula (I). In another aspect, there is provided a pharmaceutical composition comprising a compound as defined herein and at least one of a pharmaceutically acceptable carrier, a pharmaceutically acceptable excipient, and a pharmaceutically acceptable diluent. It will be clear this also applies to intermediates of Formula (A).

Also provided are processes for making a pharmaceutical composition comprising, consisting of, and/or consisting essentially of admixing a compound of Formula (I), and a pharmaceutically acceptable carrier, a pharmaceutically acceptable excipient, and/or a pharmaceutically acceptable diluent. It will be clear this also applies to intermediates of Formula (A).

The present disclosure further provides methods for treating or ameliorating a disease, syndrome, condition, or disorder in a subject, including a mammal and/or human in which the disease, syndrome, or condition is affected by the inhibition of MALT1, including but not

limited to, cancer and/or immunological diseases, using a compound of Formula (I). It will be clear this also applies to intermediates of Formula (A).

In another aspect, there is provided a compound as defined herein or a pharmaceutical composition as defined herein for use as a medicament.

The present disclosure also is directed to the use of any of the compounds described herein in the preparation of a medicament wherein the medicament is prepared for treating a disease, syndrome, condition, or disorder that is affected by the inhibition of MALT1, such as cancer and/or immunological diseases.

In another aspect, there is provided use of a compound as defined herein or a pharmaceutical composition as defined herein in the manufacture of a medicament for the treatment or prevention of cancer or an immunological disease.

The present disclosure is also directed to the preparation of compounds of Formula (I) that act as an inhibitor of MALT1. The present disclosure is also directed to the preparation of intermediates of Formula (A) that act as an inhibitor of MALT1.

Exemplifying the disclosure are methods of treating a disease, syndrome, condition, or disorder mediated by MALT1, using a compound of Formula (I). In particular said disease, syndrome, condition, or disorder mediated by MALT1 is selected from the group consisting of lymphomas, leukemias, carcinomas, and sarcomas, e.g. non-Hodgkin's lymphoma (NHL (including B-cell NHL)), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), mucosa-associated lymphoid tissue (MALT) lymphoma, marginal zone lymphoma, T-cell lymphoma, Hodgkin's lymphoma, Burkitt's lymphoma, multiple myeloma, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), Waldenström macroglobulinemia, lymphoblastic T cell leukemia, chronic myelogenous leukemia (CML), hairy-cell leukemia, acute lymphoblastic T cell leukemia, plasmacytoma, immunoblastic large cell leukemia, megakaryoblastic leukemia, acute megakaryocytic leukemia, promyelocytic leukemia, erytholeukemia, brain (gliomas), glioblastomas, breast cancer, colorectal/colon cancer, prostate cancer, lung cancer including non-small-cell, gastric cancer, endometrial cancer, melanoma, pancreatic cancer, liver cancer, kidney cancer, squamous cell carcinoma, ovarian cancer, sarcoma, osteosarcoma, thyroid cancer, bladder cancer, head and neck cancer, testicular cancer, Ewing's sarcoma, rhabdomyosarcoma, medulloblastoma, neuroblastoma, cervical cancer, renal cancer, urothelial cancer, vulval cancer, esophageal cancer, salivary gland cancer, nasopharangeal cancer, buccal cancer, cancer of the mouth, and GIST (gastrointestinal stromal tumor), comprising, consisting of, and/or consisting essentially of, administering to a subject in need thereof a therapeutically effective amount of any of the compounds or pharmaceutical compositions described in the present disclosure

In another example, the disease, syndrome, condition, or disorder mediated by MALT1 is selected from the group consisting of diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), and mucosa-associated lymphoid tissue (MALT) lymphoma.

An example of the present disclosure is directed to a compound of Formula (I) for (use in) the treatment of immunological diseases that are affected by the inhibition of MALT1,

including but not limited to, autoimmune and inflammatory disorders, e.g. arthritis, inflammatory bowel disease, gastritis, ankylosing spondylitis, ulcerative colitis, pancreatits, Crohn's disease, celiac disease, multiple sclerosis, systemic lupus erythematosus, lupus nephritis, rheumatic fever, gout, organ or transplact rejection, chronic allograft rejection, acute or chronic graft-versus-host disease, dermatitis including atopic, dermatomyositis, psoriasis, Behcet's diseases, uveitis, myasthenia gravis, Grave's disease, Hashimoto thyroiditis, Sjorgen's syndrome, blistering disorders, antibody-mediated vasculitis syndromes, immune-complex vasculitides, allergic disorders, asthma, bronchitis, chronic obstructive pulmonary disease (COPD), cystic fibrosis, pneumonia, pulmonary diseases including oedema, embolism, fibrosis, sarcoidosis, hypertension and emphysema, silicosis, respiratory failure, acute respiratory distress syndrome, BENTA disease, berylliosis, and polymyositis.

In another example, the present disclosure is directed to a compound of Formula (I) for (use in) the treatment of a disease, syndrome, condition, or disorder affected by inhibition of MALT1, selected from the group consisting of rheumatoid arthritis (RA), psoritic arthritis (PsA), psorisis (Pso), ulcerative colitis (UC), Crohn's disease, systemic lupus erythematosus (SLE), asthma, and chronic obstructive pulmonary disease (COPD).

In an alternate example, the disease, syndrome, condition, or disorder affected by inhibition of MALT1 is selected from non-Hodgkin's lymphoma (NHL), diffuse large B-cell lymphoma (DLBCL), marginal zone lymphoma, mantle cell lymphoma (MCL), follicular lymphoma (FL), transformed follicular lymphoma, chronic lymphocytic leukemia, and Waldenström macroglobulinemia.

In yet another example of the disclosure, the disease, syndrome, condition, or disorder affected by inhibition of MALT1 is lymphoma.

In another example of the disclosure, the disease, syndrome, condition, or disorder affected by inhibition of MALT1 is the activated B cell like (ABC) subtype of diffuse large B-cell lymphoma (DLBCL).

In another example of the disclosure, the disease, syndrome, condition, or disorder affected by inhibition of MALT1 is germinal center B cell like (GCB) subtype of diffuse large B-cell lymphoma (DLBCL).

In another example of the disclosure, the disease, syndrome, condition, or disorder affected by inhibition of MALT1 is non-germinal center B cell like (non-GCB) subtype of diffuse large B-cell lymphoma (DLBCL).

In an additional example of the disclosure, the disease, syndrome, condition, or disorder affected by inhibition of MALT1 is chronic lymphocytic leukemia (CLL). In another example, the disorder or condition small lymphocytic lymphoma (SLL).

In another example of the disclosure, the lymphoma is MALT lymphoma.

In another example of the disclosure, the disease, syndrome, condition, or disorder affected by inhibition of MALT1 is Waldenström macroglobulinemia (WM).

In yet another example, the disease, syndrome, condition, or disorder affected by inhibition of MALT1 is selected from the group consisting of diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), and mucosa-associated lymphoid tissue (MALT) lymphoma.

In an alternate example, the disease, syndrome, condition, or disorder affected by inhibition of MALT1 is non-Hodgkin's lymphoma (NHL). In a further example, the non-Hodgkin's lymphoma (NHL) is B-cell NHL. In another example, the non-Hodgkin's lymphoma (NHL) is relapsed/refractory B-cell NHL.

In another example of the disclosure, the disease, syndrome, condition, or disorder affected by inhibition of MALT1 is selected from the group consisting of relapsed/refractory non-germinal center B cell like (non-GCB) subtype of diffuse large B-cell lymphoma (DLBCL), relapsed/refractory Waldenström macroglobulinemia (WM), relapsed/refractory mantle cell lymphoma (MCL), relapsed/refractory follicular lymphoma (FL), and relapsed/refractory mucosa-associated lymphoid tissue (MALT) lymphoma.

In another example of the disclosure, the disease, syndrome, condition, or disorder affected by inhibition of MALT1 is relapsed/refractory non-germinal center B cell like (non-GCB) subtype of diffuse large B-cell lymphoma (DLBCL).

In another example of the disclosure, the disease, syndrome, condition, or disorder affected by inhibition of MALT1 is relapsed/refractory Waldenström macroglobulinemia (WM).

In another example of the disclosure, the disease, syndrome, condition, or disorder affected by inhibition of MALT1 is relapsed/refractory mantle cell lymphoma (MCL).

In another example of the disclosure, the disease, syndrome, condition, or disorder affected by inhibition of MALT1 is relapsed/refractory follicular lymphoma (FL).

In another example of the disclosure, the disease, syndrome, condition, or disorder affected by inhibition of MALT1 is relapsed/refractory mucosa-associated lymphoid tissue (MALT) lymphoma.

Compounds of Formula (I) may be used for the treatment of immunological diseases including, but not limited to, autoimmune and inflammatory disorders, e.g. sepsis-related acute lung injury (ALI), acute respiratory distress syndrome (ARDS), arthritis, rheumatoid arthritis (RA), psoriatic arthritis (PsA), inflammatory bowel disease, gastritis, ankylosing spondylitis, ulcerative colitis, pancreatitis, Crohn's disease, celiac disease, multiple sclerosis, systemic lupus erythematosus, lupus nephritis, rheumatic fever, gout, organ or transplant rejection,

chronic allograft rejection, acute or chronic graft-versus-host disease, dermatitis including atopic, dermatomyositis, psoriasis, Behcet's diseases, uveitis, myasthenia gravis, Grave's disease, Hashimoto thyroiditis, Sjorgen's syndrome, blistering disorders, antibody-mediated vasculitis syndromes, immune-complex vasculitides, allergic disorders, asthma, bronchitis, chronic obstructive pulmonary disease (COPD), cystic fibrosis, pneumonia, pulmonary diseases including oedema, embolism, fibrosis, sarcoidosis, hypertension and emphysema, silicosis, respiratory failure, acute respiratory distress syndrome, BENTA disease, berylliosis, and polymyositis.

In another example of the present disclosure, the compounds of the present disclosure may be employed in combination with one or more other medicinal agents, more particularly with other anti-cancer agents, e.g. chemotherapeutic, anti-proliferative or immunomodulating agents, or with adjuvants in cancer therapy, e.g. immunosuppressive or anti-inflammatory agents.

Possible combinations of the compounds of the present disclosure may include, but are not limited to, BTK (Bruton's tyrosine kinase) inhibitors such as ibrutinib, SYK inhibitors, PKC inhibitors, PI3K pathway inhibitors, BCL family inhibitors, JAK inhibitors, 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-PD1 antibodies, and anti-PD-L1 antibodies.

It will be appreciated that variations to the foregoing examples of the disclosure can be made while still falling within the scope of the disclosure. Each feature disclosed in this specification, unless stated otherwise, may be replaced by alternative features serving the same, equivalent or similar purpose. Thus, unless stated otherwise, each feature disclosed is one example only of a generic series of equivalent or similar features.

All possible combinations of the above-indicated examples are considered to be embraced within the scope of this disclosure.

In another example, the present disclosure is directed to a compound of Formula (I) for (use in) the treatment of said disease, syndrome, condition, or disorder affected by the inhibition of MALT1.

In another example, the present disclosure is directed to a composition comprising a compound of Formula (I) for (use in) the treatment of said disease, syndrome, condition, or disorder affected by inhibition of MALT1.

In another example, the present disclosure is directed to methods of treating said disease, syndrome, condition, or disorder mediated by MALT1.

Another example of the present disclosure is directed to a pharmaceutical composition comprising a compound of Formula (I) and uses thereof as described in any of the other examples.

DETAILED DESCRIPTION OF THE INVENTION

With reference to substituents, the term "independently" refers to the situation where several substituents are selected independently from each other and may be the same or different from each other.

The term "about" means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system. Unless explicitly stated otherwise within the Examples or elsewhere in the Specification in the context of a particular assay, result or embodiment, "about" means within one standard deviation per the practice in the art, or a range of up to 5%, whichever is larger.

The transitional terms "comprising," "consisting essentially of," and "consisting of" are intended to connote their generally accepted meanings in the patent vernacular; that is, (i) "comprising," which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps; (ii) "consisting of" excludes any element, step, or ingredient not specified in the claim; and (iii) "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. Embodiments described in terms of the phrase "comprising" (or its equivalents) also provide as embodiments those independently described in terms of "consisting of" and "consisting essentially of."

The prefix 'C_{x-y}' (where x and y are integers) as used herein refers to the number of carbon atoms in a given group. Thus, a C_{1-4}alkyl group contains from 1 to 4 carbon atoms, and so on.

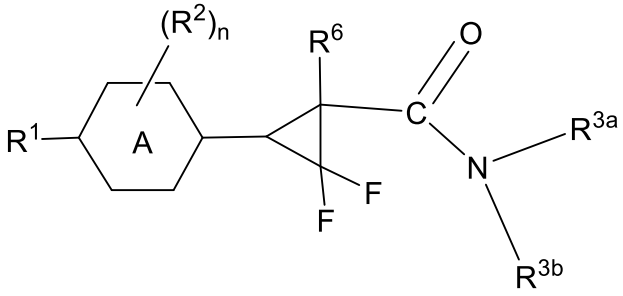
The term 'C_{1-4}alkyl' as used herein as a group or part of a group represents a straight or branched chain saturated hydrocarbon radical having from 1 to 4 carbon atoms, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *s*-butyl, *t*-butyl and the like.

The term 'C_{3-6}cycloalkyl' as used herein as a group or part of a group defines a saturated, cyclic hydrocarbon radical having from 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Fused bicycles or fused bicyclic groups, are two cycles that share two atoms and the bond between these atoms.

CLAIMS

1. A compound of Formula (I)

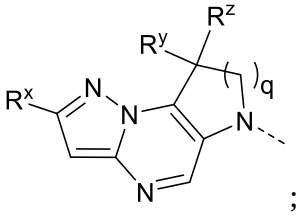


(I)

Formula (I)

or a tautomer or a stereoisomeric form thereof, wherein

R^1 represents



;

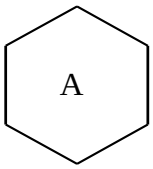
q is 1 or 2;

R^x represents hydrogen; C_{1-4}alkyl; halo; or C_{1-4}alkyl substituted with one, two or three halo substituents;

R^y represents hydrogen; C_{1-4}alkyl; C_{3-6}cycloalkyl; or C_{1-4}alkyl substituted with one, two or three halo substituents;

R^z represents C_{1-4}alkyl; C_{3-6}cycloalkyl; or C_{1-4}alkyl substituted with one, two or three halo substituents;

or R^y and R^z taken together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

ring 

represents phenyl or pyridyl;

R^2 represents halo;

n is 0, 1 or 2;

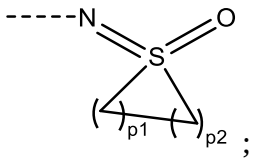
R^{3a} represents hydrogen or C_{1-4}alkyl;

R^{3b} represents hydrogen; C_{1-4}alkyl; C_{3-6}cycloalkyl; adamantyl; C_{6-10}carbobicyclic; Het^1;

C_{3-6}cycloalkyl substituted with one, two, three or four substituents each independently selected from the group consisting of oxo, halo, cyano, -OH, -OR^7, -$S(=O)_2$-R^7, -$S(=O)_2$-$NR^{4a}R^{4b}$, -$NR^{4a}R^{4b}$, -S(=O)(=NH)-R^7, -N=S(=O)-$(C_{1-4}alkyl)_2$, -NH-(C=O)-R^7, -C(=O)-$NR^{4a}R^{4b}$, -S(=O)(=NH)-$NR^{4a}R^{4b}$, -P(=O)-$R^{4c}R^{4d}$, -O-C_{1-4}alkyl-C(=O)-$NR^{4a}R^{4b}$, -S(=O)(=NH)-C_{1-4}alkyl-O-R^7, -NH-$S(=O)_2$-R^7, Het^{3a}, Het^{3b}, and C_{1-4}alkyl optionally substituted with one, two or three substituents each independently selected from the group consisting of -OH, halo, -S(=O)(=NH)-C_{1-4}alkyl, -C(=O)-$NR^{4a}R^{4b}$, -$S(=O)_2$-$NR^{4a}R^{4b}$, and -$S(=O)_2$-C_{1-4}alkyl;

C_{6-10}carbobicyclic substituted with one, two, three or four substituents each independently selected from the group consisting of oxo, halo, cyano, -OH, -OR^7, -$S(=O)_2$-R^7, -$S(=O)_2$-$NR^{4a}R^{4b}$, -$NR^{4a}R^{4b}$, -S(=O)(=NH)-R^7, -N=S(=O)-$(C_{1-4}alkyl)_2$, -NH-(C=O)-R^7, -C(=O)-$NR^{4a}R^{4b}$, -S(=O)(=NH)-$NR^{4a}R^{4b}$, -P(=O)-$R^{4c}R^{4d}$, -O-C_{1-4}alkyl-C(=O)-$NR^{4a}R^{4b}$, -S(=O)(=NH)-C_{1-4}alkyl-O-R^7, -NH-$S(=O)_2$-R^7, and C_{1-4}alkyl optionally substituted with one, two or three substituents each independently selected from the group consisting of -OH, halo, -S(=O)(=NH)-C_{1-4}alkyl, -C(=O)-$NR^{4a}R^{4b}$, -$S(=O)_2$-$NR^{4a}R^{4b}$, and -$S(=O)_2$-C_{1-4}alkyl; or

C_{1-4}alkyl substituted with one, two, three or four substituents each independently selected from the group consisting of cyano, halo, -OH, -OR^7, -$S(=O)_2$-R^7, -$S(=O)_2$-$NR^{4a}R^{4b}$, -$NR^{4a}R^{4b}$, -S(=O)(=NH)-R^7, -N=S(=O)-$(C_{1-4}alkyl)_2$, -NH-(C=O)-R^7, -C(=O)-$NR^{4a}R^{4b}$, -S(=O)(=NH)-$NR^{4a}R^{4b}$, -P(=O)-$R^{4c}R^{4d}$, -O-C_{1-4}alkyl-C(=O)-$NR^{4a}R^{4b}$, -S(=O)(=NH)-C_{1-4}alkyl-O-R^7, -NH-$S(=O)_2$-R^7, -CF_3, Cy^1, Het^{3a}, Het^{3b}, -O-Het^{3b}, -C(=O)-Het^{3a}, -C(=O)-Het^{3b}, and



;

or R^{3a} and R^{3b} are taken together to form together with the nitrogen atom to which they are attached Het^2;

Cy^1 represents C_{3-6}cycloalkyl; or C_{3-6}cycloalkyl substituted with one, two or three substituents each independently selected from the group consisting of halo, -OH, -OR^7, -$S(=O)_2$-C_{1-4}alkyl, -$S(=O)_2$-$NR^{4a}R^{4b}$, -$NR^{4a}R^{4b}$, -S(=O)(=NH)-C_{1-4}alkyl, -N=S(=O)-$(C_{1-4}alkyl)_2$, -NH-(C=O)-C_{1-4}alkyl, -NH-(C=O)-C_{3-6}cycloalkyl, -C(=O)-$NR^{4a}R^{4b}$, and -NH-$S(=O)_2$-R^7;

Het^1 represents a monocyclic C-linked 4- to 7-membered fully saturated heterocyclyl containing one, two or three heteroatoms each independently selected from O, S, and N; or Het^1 represents a bicyclic C-linked 6- to 11-membered fully saturated heterocyclyl containing one, two or three heteroatoms each independently selected from O, S, and N;

wherein one or more of the carbon atoms in said heterocyclyl might be substituted with in total one, two or three substituents each independently selected from the group consisting of oxo, halo, cyano, -OH, -OR^7 -$S(=O)_2$-R^7, -$S(=O)_2$-$NR^{4a}R^{4b}$, -$NR^{4a}R^{4b}$, -S(=O)(=NH)-R^7, -N=S(=O)-$(C_{1-4}alkyl)_2$, -NH-(C=O)-R^7, -C(=O)-$NR^{4a}R^{4b}$, -S(=O)(=NH)-$NR^{4a}R^{4b}$, -P(=O)-$R^{4c}R^{4d}$, -O-C_{1-4}alkyl-C(=O)-$NR^{4a}R^{4b}$, -S(=O)(=NH)-C_{1-4}alkyl-O-R^7, -NH-$S(=O)_2$-R^7, and C_{1-4}alkyl optionally substituted with one, two or three substituents each independently selected from the group consisting of -OH, halo, -S(=O)(=NH)-C_{1-4}alkyl, -C(=O)-$NR^{4a}R^{4b}$, -$S(=O)_2$-$NR^{4a}R^{4b}$, and -$S(=O)_2$-C_{1-4}alkyl;

wherein one or more of the S-atoms in said heterocyclyl might be substituted to form S(=O), $S(=O)_2$, or S(=O)(=NH);

wherein one or more of the N-atoms in said heterocyclyl might be substituted with C_{1-4}alkyl, Het^5, -C(=O)-$NR^{4a}R^{4b}$, -C(=O)-C_{1-4}alkyl, -$S(=O)_2$-C_{1-4}alkyl, -$S(=O)_2$-$NR^{4a}R^{4b}$, -C(=O)-C_{3-6}cycloalkyl, or C_{1-4}alkyl substituted with one, two or three substituents each independently selected from the group consisting of -OH and halo;

Het^2 represents a monocyclic N-linked 4- to 7-membered fully saturated heterocyclyl containing one N-atom and optionally one or two heteroatoms each independently selected from O, S, and N; or Het^2 represents a bicyclic N-linked 6- to 11-membered fully saturated heterocyclyl containing one N-atom and optionally one or two heteroatoms each independently selected from O, S, and N;

wherein one or more of the carbon atoms in said heterocyclyl might be substituted with in total one, two or three substituents each independently selected from the group consisting of oxo, halo, cyano, -OH, -OR^7, Het^6, -$S(=O)_2$-R^7, -$S(=O)_2$-$NR^{4a}R^{4b}$, -$NR^{4a}R^{4b}$, -S(=O)(=NH)-R^7, -N=S(=O)-$(C_{1-4}alkyl)_2$, -NH-(C=O)-R^7, -C(=O)-$NR^{4a}R^{4b}$, -S(=O)(=NH)-$NR^{4a}R^{4b}$, -P(=O)-$R^{4c}R^{4d}$, -O-C_{1-4}alkyl-C(=O)-$NR^{4a}R^{4b}$, -S(=O)(=NH)-C_{1-4}alkyl-O-R^7, -NH-$S(=O)_2$-R^7, and C_{1-4}alkyl optionally substituted with one, two or three substituents each independently selected from the group consisting of -OH, halo, -S(=O)(=NH)-C_{1-4}alkyl, -C(=O)-$NR^{4a}R^{4b}$, -$S(=O)_2$-$NR^{4a}R^{4b}$, Het^4 and -$S(=O)_2$-C_{1-4}alkyl;

wherein one or more of the S-atoms in said heterocyclyl might be substituted to form S(=O), $S(=O)_2$, or S(=O)(=NH);

wherein one or more of the N-atoms in said heterocyclyl might be substituted with C_{1-4}alkyl, -C(=O)-$NR^{4a}R^{4b}$, -C(=O)-C_{1-4}alkyl, -$S(=O)_2$-C_{1-4}alkyl, -$S(=O)_2$-$NR^{4a}R^{4b}$, Het^4, or -C(=O)-C_{3-6}cycloalkyl;

Het^{3a} represents a monocyclic N-linked 4- to 7-membered fully saturated heterocyclyl

containing one N-atom and optionally one or two heteroatoms each independently selected from O, S, and N; or Het^{3a} represents a bicyclic N-linked 6- to 11-membered fully saturated heterocyclyl containing one N-atom and optionally one or two heteroatoms each independently selected from O, S, and N;

wherein one or more of the carbon atoms in said heterocyclyl might be substituted with in total one, two or three substituents each independently selected from the group consisting of oxo, halo, -OH, $-OR^7$, $-S(=O)_2-C_{1-4}$alkyl, $-S(=O)_2-NR^{4a}R^{4b}$, $-NR^{4a}R^{4b}$, $-S(=O)(=NH)-C_{1-4}$alkyl, $-N=S(=O)-(C_{1-4}alkyl)_2$, $-NH-(C=O)-C_{1-4}$alkyl, $-NH-(C=O)-C_{3-6}$cycloalkyl, $-C(=O)-NR^{4a}R^{4b}$, and $-NH-S(=O)_2-R^7$;

wherein one or more of the S-atoms in said heterocyclyl might be substituted to form S(=O), $S(=O)_2$, or S(=O)(=NH);

wherein one or more of the N-atoms in said heterocyclyl might be substituted with C_{1-4}alkyl, Het^5, $-C(=O)-NR^{4a}R^{4b}$, $-C(=O)-C_{1-4}$alkyl, $-S(=O)_2-C_{1-4}$alkyl, $-S(=O)_2-NR^{4a}R^{4b}$, $-C(=O)-C_{3-6}$cycloalkyl, or C_{1-4}alkyl substituted with one, two or three substituents each independently selected from the group consisting of -OH and halo;

Het^{3b} represents a monocyclic C-linked 4- to 7-membered fully saturated heterocyclyl containing one, two or three heteroatoms each independently selected from O, S, and N; or Het^{3b} represents a bicyclic C-linked 6- to 11-membered fully saturated heterocyclyl containing one, two or three heteroatoms each independently selected from O, S, and N;

wherein one or more of the carbon atoms in said heterocyclyl might be substituted with in total one, two or three substituents each independently selected from the group consisting of oxo, halo, -OH, C_{1-4}alkyl, $-OR^7$, $-S(=O)_2-C_{1-4}$alkyl, $-S(=O)_2-NR^{4a}R^{4b}$, $-NR^{4a}R^{4b}$, $-S(=O)(=NH)-C_{1-4}$alkyl, $-N=S(=O)-(C_{1-4}alkyl)_2$, $-NH-(C=O)-C_{1-4}$alkyl, $-NH-(C=O)-C_{3-6}$cycloalkyl, $-C(=O)-NR^{4a}R^{4b}$, and $-NH-S(=O)_2-R^7$;

wherein one or more of the S-atoms in said heterocyclyl might be substituted to form S(=O), $S(=O)_2$, or S(=O)(=NH);

wherein one or more of the N-atoms in said heterocyclyl might be substituted with C_{1-4}alkyl, Het^5, $-C(=O)-NR^{4a}R^{4b}$, $-C(=O)-C_{1-4}$alkyl, $-S(=O)_2-C_{1-4}$alkyl, $-S(=O)_2-NR^{4a}R^{4b}$, $-C(=O)-C_{3-6}$cycloalkyl, or C_{1-4}alkyl substituted with one, two or three substituents each independently selected from the group consisting of -OH and halo;

Het^4 represents a monocyclic C-linked 4- to 7-membered fully saturated heterocyclyl containing one, two or three heteroatoms each independently selected from O, S, and N;

wherein one or more of the S-atoms in said heterocyclyl might be substituted to form S(=O), $S(=O)_2$, or S(=O)(=NH);

Het^5 represents a monocyclic C-linked 4- to 7-membered fully saturated heterocyclyl containing one, two or three heteroatoms each independently selected from O, S, and N;

wherein one or more of the S-atoms in said heterocyclyl might be substituted to form S(=O),

$S(=O)_2$, or S(=O)(=NH);

Het^6 represents a monocyclic N-linked 4- to 7-membered fully saturated heterocyclyl containing one N-atom and optionally one or two heteroatoms each independently selected from O, S, and N;
wherein one or more of the S-atoms in said heterocyclyl might be substituted to form S(=O), $S(=O)_2$, or S(=O)(=NH);

R^{4a} and R^{4b} each independently represent hydrogen, C_{1-4}alkyl, C_{3-6}cycloalkyl, or C_{1-4}alkyl-O-C_{1-4}alkyl;

R^{4c} and R^{4d} each independently represent C_{1-4}alkyl or -O-C_{1-4}alkyl;

R^6 represents C_{1-4}alkyl; or C_{1-4}alkyl substituted with one -OH;

R^7 represents C_{1-4}alkyl or C_{3-6}cycloalkyl, each optionally substituted with one, two or three halo substituents;

p1 and p2 each independently are 1, 2 or 3;

or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1 wherein

R^x represents halo;

R^y represents hydrogen or C_{1-4}alkyl;

R^z represents C_{1-4}alkyl substituted with one, two or three halo substituents;

or R^y and R^z taken together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

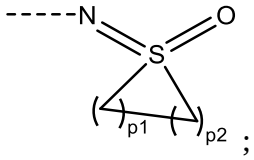
R^{3b} represents hydrogen; C_{1-4}alkyl; C_{3-6}cycloalkyl; adamantyl; C_{6-10}carbobicyclic; Het^1;

C_{3-6}cycloalkyl substituted with one, two, three or four substituents each independently selected from the group consisting of oxo, -OH, $-OR^7$, $-S(=O)_2-R^7$, $-S(=O)_2-NR^{4a}R^{4b}$, $-NR^{4a}R^{4b}$, $-S(=O)(=NH)-R^7$, $-NH-(C=O)-R^7$, $-S(=O)(=NH)-NR^{4a}R^{4b}$, $-P(=O)-R^{4c}R^{4d}$, $-NH-S(=O)_2-R^7$, Het^{3a}, Het^{3b}, and C_{1-4}alkyl optionally substituted with one, two or three substituents each independently selected from the group consisting of -OH, halo, $-S(=O)(=NH)-C_{1-4}$alkyl, $-C(=O)-NR^{4a}R^{4b}$, $-S(=O)_2-NR^{4a}R^{4b}$, and $-S(=O)_2-C_{1-4}$alkyl;

C_{6-10}carbobicyclic substituted with one, two, three or four substituents each independently selected from the group consisting of $-OR^7$, $-S(=O)_2-R^7$, and $-S(=O)_2-NR^{4a}R^{4b}$; or

C_{1-4}alkyl substituted with one, two, three or four substituents each independently selected from the group consisting of cyano, halo, -OH, $-OR^7$, $-S(=O)_2-R^7$, $-S(=O)_2-NR^{4a}R^{4b}$, $-NR^{4a}R^{4b}$, $-S(=O)(=NH)-R^7$, $-N=S(=O)-(C_{1-4}alkyl)_2$, $-C(=O)-NR^{4a}R^{4b}$, $-P(=O)-R^{4c}R^{4d}$, $-O-C_{1-4}alkyl-C(=O)-NR^{4a}R^{4b}$, $-S(=O)(=NH)-C_{1-4}alkyl-O-R^7$, $-NH-S(=O)_2-R^7$, $-Cy^1$, Het^{3a},

Het^{3b}, -O-Het^{3b}, -C(=O)-Het^{3a}, and



;

or R^{3a} and R^{3b} are taken together to form together with the nitrogen atom to which they are attached Het^2;

Cy^1 represents C_{3-6}cycloalkyl; or C_{3-6}cycloalkyl substituted with one, two or three substituents each independently selected from the group consisting of -S(=O)$_2$-C_{1-4}alkyl, and -S(=O)$_2$-$NR^{4a}R^{4b}$;

Het^1 represents a monocyclic C-linked 4- to 7-membered fully saturated heterocyclyl containing one, two or three heteroatoms each independently selected from O, S, and N; or Het^1 represents a bicyclic C-linked 6- to 11-membered fully saturated heterocyclyl containing one, two or three heteroatoms each independently selected from O, S, and N;
wherein one or more of the carbon atoms in said heterocyclyl might be substituted with in total one, two or three substituents each independently selected from the group consisting of oxo, -OH, -OR^7 -S(=O)$_2$-R^7, -C(=O)-$NR^{4a}R^{4b}$, -S(=O)(=NH)-$NR^{4a}R^{4b}$, -P(=O)-$R^{4c}R^{4d}$, -O-C_{1-4}alkyl-C(=O)-$NR^{4a}R^{4b}$, and C_{1-4}alkyl optionally substituted with one, two or three substituents each independently selected from the group consisting of -OH, and -C(=O)-$NR^{4a}R^{4b}$;
wherein one or more of the S-atoms in said heterocyclyl might be substituted to form S(=O), S(=O)$_2$, or S(=O)(=NH);
wherein one or more of the N-atoms in said heterocyclyl might be substituted with C_{1-4}alkyl, Het^5, -C(=O)-C_{1-4}alkyl, -S(=O)$_2$-C_{1-4}alkyl, -S(=O)$_2$-$NR^{4a}R^{4b}$, -C(=O)-C_{3-6}cycloalkyl, or C_{1-4}alkyl substituted with one, two or three -OH;

Het^2 represents a monocyclic N-linked 4- to 7-membered fully saturated heterocyclyl containing one N-atom and optionally one or two heteroatoms each independently selected from O, S, and N; or Het^2 represents a bicyclic N-linked 6- to 11-membered fully saturated heterocyclyl containing one N-atom and optionally one or two heteroatoms each independently selected from O, S, and N;
wherein one or more of the carbon atoms in said heterocyclyl might be substituted with in total one, two or three substituents each independently selected from the group consisting of Het^6, -S(=O)$_2$-$NR^{4a}R^{4b}$, -S(=O)(=NH)-R^7, -N=S(=O)-(C_{1-4}alkyl)$_2$, -C(=O)-$NR^{4a}R^{4b}$, and C_{1-4}alkyl optionally substituted with one, two or three -S(=O)$_2$-C_{1-4}alkyl;
wherein one or more of the S-atoms in said heterocyclyl might be substituted to form S(=O),

$S(=O)_2$, or S(=O)(=NH);
wherein one or more of the N-atoms in said heterocyclyl might be substituted with Het^4;

Het^{3a} represents a monocyclic N-linked 4- to 7-membered fully saturated heterocyclyl containing one N-atom and optionally one or two heteroatoms each independently selected from O, S, and N;
wherein one or more of the carbon atoms in said heterocyclyl might be substituted with in total one, two or three substituents each independently selected from the group consisting of oxo, and -OH;
wherein one or more of the S-atoms in said heterocyclyl might be substituted to form S(=O), $S(=O)_2$, or S(=O)(=NH);
wherein one or more of the N-atoms in said heterocyclyl might be substituted with $C_{1\text{-}4}$alkyl, Het^5, -C(=O)-$C_{1\text{-}4}$alkyl, -$S(=O)_2$-$C_{1\text{-}4}$alkyl, -$S(=O)_2$-$NR^{4a}R^{4b}$, or -C(=O)-$C_{3\text{-}6}$cycloalkyl;

Het^{3b} represents a monocyclic C-linked 4- to 7-membered fully saturated heterocyclyl containing one, two or three heteroatoms each independently selected from O, S, and N; or
Het^{3b} represents a bicyclic C-linked 6- to 11-membered fully saturated heterocyclyl containing one, two or three heteroatoms each independently selected from O, S, and N;
wherein one or more of the carbon atoms in said heterocyclyl might be substituted with in total one, two or three substituents each independently selected from the group consisting of oxo, halo, -OH, $C_{1\text{-}4}$alkyl, and -OR^7;
wherein one or more of the S-atoms in said heterocyclyl might be substituted to form S(=O), $S(=O)_2$, or S(=O)(=NH);
wherein one or more of the N-atoms in said heterocyclyl might be substituted with $C_{1\text{-}4}$alkyl, Het^5, or -$S(=O)_2$-$C_{1\text{-}4}$alkyl;

Het^4 represents a monocyclic C-linked 4- to 7-membered fully saturated heterocyclyl containing one, two or three heteroatoms each independently selected from O, S, and N;
wherein one or more of the S-atoms in said heterocyclyl might be substituted to form S(=O), $S(=O)_2$, or S(=O)(=NH);
Het^5 represents a monocyclic C-linked 4- to 7-membered fully saturated heterocyclyl containing one, two or three heteroatoms each independently selected from O, S, and N;
wherein one or more of the S-atoms in said heterocyclyl might be substituted to form S(=O), $S(=O)_2$, or S(=O)(=NH);

Het^6 represents a monocyclic N-linked 4- to 7-membered fully saturated heterocyclyl containing one N-atom and optionally one or two heteroatoms each independently selected from O, S, and N;

wherein one or more of the S-atoms in said heterocyclyl might be substituted to form S(=O), $S(=O)_2$, or S(=O)(=NH);

p1 and p2 are 2.

3. The compound according to claim 1 or 2 wherein

q is 1;

R^x represents halo;

R^y represents C_{1-4}alkyl;

R^z represents C_{1-4}alkyl substituted with one, two or three halo substituents;

n is 0 or 1;

R^{3a} represents hydrogen;

R^{3b} represents C_{1-4}alkyl; C_{3-6}cycloalkyl; or

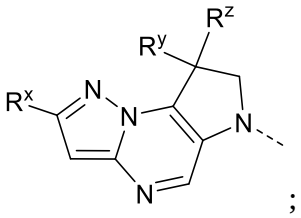
C_{3-6}cycloalkyl substituted with one substituent selected from the group consisting of $-S(=O)_2-R^7$ and $-S(=O)(=NH)-R^7$;

R^6 represents C_{1-4}alkyl; or C_{1-4}alkyl substituted with one -OH;

R^7 represents C_{1-4}alkyl.

4. The compound according to claim 1 wherein

R^1 represents



;

R^y represents C_{1-4}alkyl; C_{3-6}cycloalkyl; or C_{1-4}alkyl substituted with one, two or three halo substituents;

R^z represents C_{1-4}alkyl; C_{3-6}cycloalkyl; or C_{1-4}alkyl substituted with one, two or three halo substituents;

or R^y and R^z taken together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

R^{3a} represents hydrogen; and

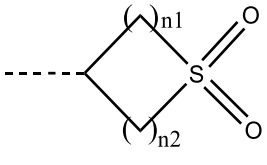
R^{3b} represents hydrogen; C_{1-4}alkyl; C_{3-6}cycloalkyl; $-C_{1-4}$alkyl-Cy^1;

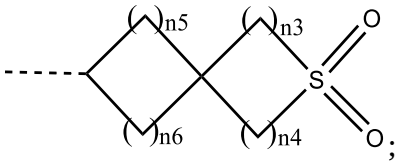
C_{3-6}cycloalkyl substituted with one substituent selected from the group consisting of halo, -OH, $-O-C_{1-4}$alkyl, $-OCF_3$, $-OCHF_2$, $-S(=O)_2-C_{1-4}$alkyl, $-S(=O)_2-NR^{4a}R^{4b}$, $-NR^{4a}R^{4b}$, $-S(=O)(=NH)-C_{1-4}$alkyl, $-N=S(=O)-(C_{1-4}alkyl)_2$, $-NH-(C=O)-C_{1-4}$alkyl,

-NH-(C=O)-C_{3-6}cycloalkyl, -C(=O)-$NR^{4a}R^{4b}$, and -NH-$S(=O)_2$-C_{1-4}alkyl;

C_{1-4}alkyl substituted with one, two or three substituents each independently selected from the group consisting of halo, -OH, -O-C_{1-4}alkyl, $-OCF_3$, $-OCHF_2$, -$S(=O)_2$-C_{1-4}alkyl, -$S(=O)_2$-$NR^{4a}R^{4b}$, -$NR^{4a}R^{4b}$, -S(=O)(=NH)-C_{1-4}alkyl, -N=S(=O)-$(C_{1-4}alkyl)_2$, -NH-(C=O)-C_{1-4}alkyl, -NH-(C=O)-C_{3-6}cycloalkyl, -C(=O)-$NR^{4a}R^{4b}$, and -NH-$S(=O)_2$-C_{1-4}alkyl;

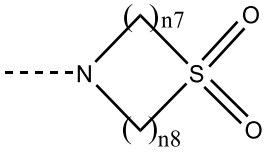
3- or 4-piperidinyl optionally substituted on the N-atom with C_{1-4}alkyl, -C(=O)-$NR^{4a}R^{4b}$, -C(=O)-C_{1-4}alkyl, -$S(=O)_2$-C_{1-4}alkyl, or -C(=O)-C_{3-6}cycloalkyl;

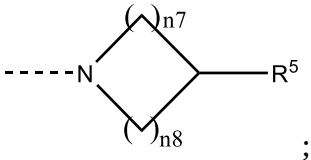


; or


;

or R^{3a} and R^{3b} are taken together to form together with the nitrogen atom to which they are attached



; or


;

Cy^1 represents C_{3-6}cycloalkyl; or C_{3-6}cycloalkyl substituted with one substituent selected from the group consisting of halo, -OH, -O-C_{1-4}alkyl, $-OCF_3$, $-OCHF_2$, -$S(=O)_2$-C_{1-4}alkyl, -$S(=O)_2$-$NR^{4a}R^{4b}$, -$NR^{4a}R^{4b}$, -S(=O)(=NH)-C_{1-4}alkyl, -N=S(=O)-$(C_{1-4}alkyl)_2$, -NH-(C=O)-C_{1-4}alkyl, -NH-(C=O)-C_{3-6}cycloalkyl, -C(=O)-$NR^{4a}R^{4b}$, and -NH-$S(=O)_2$-C_{1-4}alkyl;

R^{4a} and R^{4b} each independently represent hydrogen or C_{1-4}alkyl;

R^5 represents hydrogen, -OH, -O-C_{1-4}alkyl, -$S(=O)_2$-C_{1-4}alkyl, -$S(=O)_2$-C_{3-6}cycloalkyl, -$S(=O)_2$-$NR^{4a}R^{4b}$, or -C(=O)-$NR^{4a}R^{4b}$;

n1, n2, n3, n4, n5, n6, n7 and n8 each independently are 1 or 2;

R^6 represents methyl.

5. The compound according to claim 4 wherein

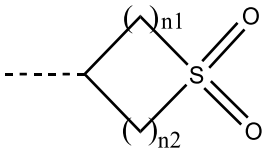
R^x represents hydrogen, C_{1-4}alkyl or halo;

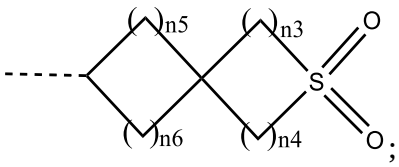
R^{3a} represents hydrogen; and

R^{3b} represents hydrogen; C_{1-4}alkyl; C_{3-6}cycloalkyl;

C_{3-6}cycloalkyl substituted with one substituent selected from the group consisting of -OH, -$S(=O)_2$-C_{1-4}alkyl, -$NR^{4a}R^{4b}$, -S(=O)(=NH)-C_{1-4}alkyl, and -N=S(=O)-$(C_{1-4}alkyl)_2$;

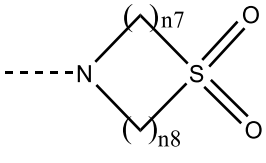
-C_{1-4}alkyl-S(=O)$_2$-C_{1-4}alkyl; C_{1-4}alkyl substituted with one, two or three halo substituents; 3- or 4-piperidinyl optionally substituted on the N-atom with C_{1-4}alkyl;

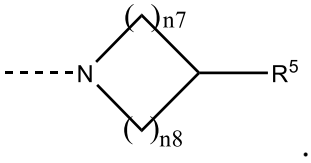


; or


;

or R^{3a} and R^{3b} are taken together to form together with the nitrogen atom to which they are attached



; or


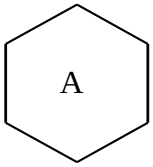
.

6. The compound according to claim 4 or 5 wherein

R^x represents halo;

R^y represents C_{1-4}alkyl;

R^z represents C_{1-4}alkyl substituted with one, two or three halo substituents;

ring 

represents phenyl;

R^2 represents halo;

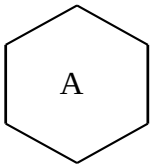
R^{3a} represents hydrogen; and

R^{3b} represents C_{1-4}alkyl; or C_{3-6}cycloalkyl substituted with one -S(=O)$_2$-C_{1-4}alkyl.

7. The compound according to any one of the preceding claims wherein n is 0.

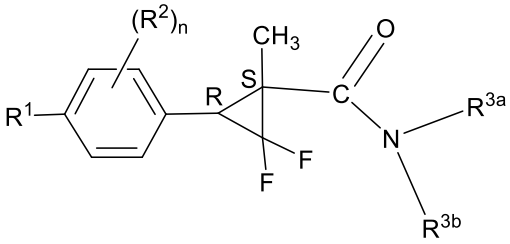
8. The compound according to any one of the preceding claims wherein n is 1.

9. The compound according to any one of the preceding claims wherein

ring 

represents phenyl, and R^6 represents methyl.

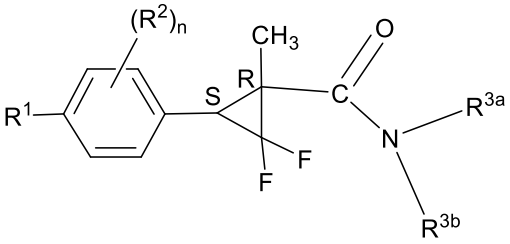
10. The compound according to any one of the preceding claims wherein Formula (I) and the stereochemistry of the substituents on the cyclopropyl moiety are as indicated below in Formula (I-a1):



(I-a1)

.

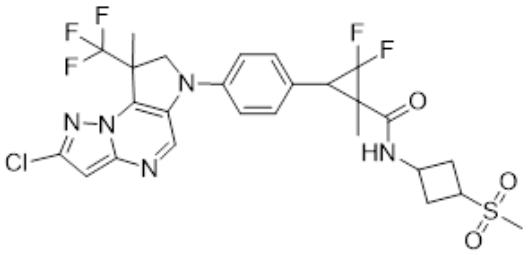
11. The compound according to any one of the preceding claims wherein Formula (I) and the stereochemistry of the substituents on the cyclopropyl moiety are as indicated below in Formula (I-b1):



(I-b1)

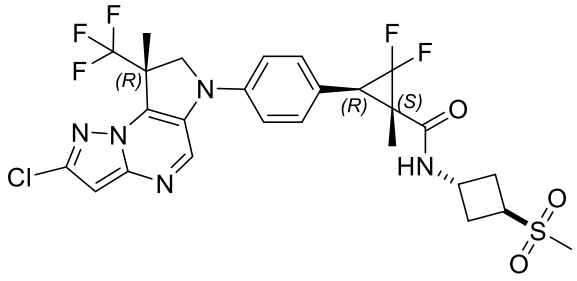
.

12. The compound according to claim 1 wherein the compound is



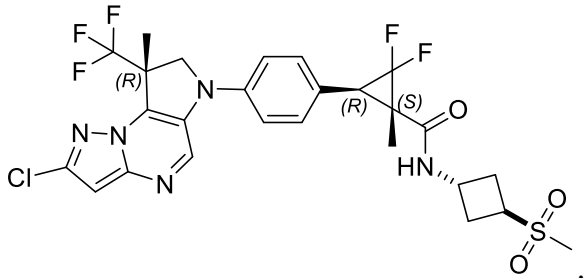
or a stereoisomeric form thereof, or a pharmaceutically acceptable salt thereof.

13. The compound according to claim 12 wherein the compound is



or a pharmaceutically acceptable salt thereof.

14. The compound according to claim 13 wherein the compound is



.

15. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 14 and at least one of a pharmaceutically acceptable carrier, a pharmaceutically acceptable excipient, and a pharmaceutically acceptable diluent.

16. A compound as claimed in any one of claims 1 to 14 or a pharmaceutical composition as claimed in claim 15 for use as a medicament.

17. Use of a compound as claimed in any one of claims 1 to 14 or a pharmaceutical composition as claimed in claim 15 in the manufacture of a medicament for the treatment or prevention of cancer or an immunological disease.

18. The use according to claim 17, wherein the cancer is non-Hodgkin's lymphoma (NHL).

19. The use according to claim 18, wherein the NHL is B-cell NHL.

20. The use according to claim 18, wherein the NHL is diffuse large B-cell lymphoma (DLBCL).

21. The use according to claim 20, wherein the DLBCL is non-germinal center B cell like (non-GCB) subtype of DLBCL.

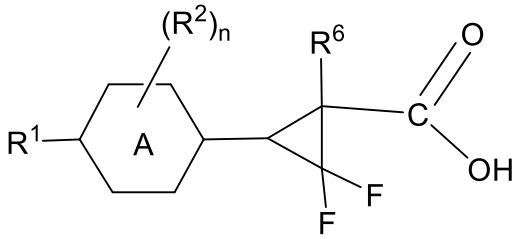
22. The use according to claim 18, wherein the NHL is mantle cell lymphoma (MCL), follicular lymphoma (FL), marginal zone lymphoma (MZL), transformed follicular lymphoma, Waldenström Macroglobulinemia or chronic lymphocytic leukemia (CLL).

23. The use according to claim 19, wherein the B-cell NHL is relapsed/refractory.

24. The use according to claim 21, wherein the non-GCB subtype of DLBCL is relapsed/refractory.

25. The use according to claim 22, wherein the NHL is relapsed/refractory.

26. A compound of Formula (A)

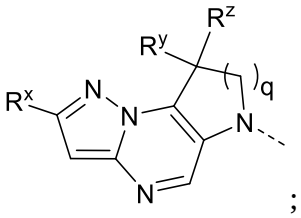


(A)

Formula (A)

or a tautomer or a stereoisomeric form thereof, wherein

R^1 represents



;

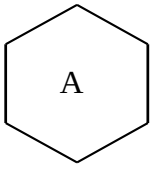
q is 1 or 2;

R^x represents hydrogen; C_{1-4}alkyl; halo; or C_{1-4}alkyl substituted with one, two or three halo substituents;

R^y represents C_{1-4}alkyl; C_{3-6}cycloalkyl; or C_{1-4}alkyl substituted with one, two or three halo substituents;

R^z represents C_{1-4}alkyl; C_{3-6}cycloalkyl; or C_{1-4}alkyl substituted with one, two or three halo substituents;

or R^y and R^z taken together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

ring 

represents phenyl or pyridyl;

R^2 represents halo;

n is 0, 1 or 2;

R^6 represents C_{1-4}alkyl; or C_{1-4}alkyl substituted with one -OH;

or a pharmaceutically acceptable salt thereof.