

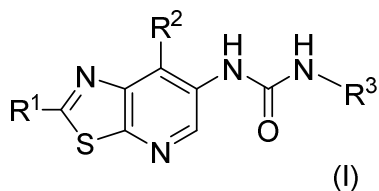
protein can have direct and indirect benefits in a variety of inflammatory disorders of multiple organs, for example, in treating psoriasis (Lowes et al, Ann Review Immunology, 32, 227-55, 2014; Afonina et al., EMBO Reports, 1-14, 2016; Howes et al., Biochem J, 1-23, 2016), multiple sclerosis (Jabara et al., J Allergy Clin Immunology, 132, 151-58, 2013; McGuire et al., J of Neuroinflammation, 11, 1-12, 2014), rheumatoid arthritis, Sjogren's syndrome (Streubel et al., Clin Cancer Research, 10, 476-80, 2004; Sagaert et al., Modern Pathology, 19, 225-32, 2006), ulcerative colitis (Liu et al., Oncotarget, 1-14, 2016), MALT lymphomas of different organs (Suzuki et al., Blood, 94, 3270-71, 1999; Akagi et al., Oncogene, 18, 5785-94, 1999) and different types of allergic disorders resulting from chronic inflammation.

In addition, several patent applications related to MALT1 are published which are as follows: WO 2008 146259, WO 2009 065897, WO 2013 017637, WO 2013 053765, WO 2014 074815, WO 2014 086478, WO 2014 207067, WO 2015 110406, WO 2015 181747, WO 2016 193339, WO 2017 040304, WO 2017 057695, and WO 2017 081641.

The foregoing shows that there exists an unmet need for MALT1 inhibitory compounds for treating diseases or disorders involving MALT1 activation, particularly cancers as well as inflammatory disorders that are dependent on the MALT1-NF- κ B axis.

SUMMARY

The present disclosure provides compounds of the general formula (I), their pharmaceutically acceptable salts, tautomeric forms, stereoisomers, polymorphs, solvates, combinations with suitable other medicament or medicaments and pharmaceutical compositions thereof and use thereof in treating various diseases or disorders including cancers.



wherein, R¹-R³ are described in detail below. The compounds of the present disclosure are potent inhibitors of MALT1.

Disclosed is a compound represented by the general formula (I), its tautomeric form, its stereoisomer, its polymorph, its solvate, its pharmaceutically acceptable salt, its combinations with suitable medicament and its pharmaceutical compositions, wherein, R¹-R³ are described in detail below.

In one aspect, there is provided 1-(6-(2H-1,2,3-Triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-3-(7-(1-methoxyethyl)-2-methylthiazolo[5,4-b]pyridin-6-yl)urea or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided (±)-1-(6-(2H-1,2,3-Triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-3-(7-(1-methoxyethyl)-2-methylthiazolo[5,4-b]pyridin-6-yl)urea or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a racemic mixture comprising the compound as described herein.

In another aspect, there is provided (+)-1-(6-(2H-1,2,3-Triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-3-(7-(1-methoxyethyl)-2-methylthiazolo[5,4-b]pyridin-6-yl)urea or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided (–)-1-(6-(2H-1,2,3-Triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-3-(7-(1-methoxyethyl)-2-methylthiazolo[5,4-b]pyridin-6-yl)urea or a pharmaceutically acceptable salt thereof.

The present disclosure provides a pharmaceutical composition, containing the compound of the general formula (I) as defined herein, its tautomeric form, and its stereoisomer, its polymorph, its solvate, its pharmaceutically acceptable salt in combination with the usual pharmaceutically employed carriers, diluents, and the like are useful for the treatment of a disease or disorder mediated through MALT1.

The present disclosure provides a pharmaceutical composition, containing the compound of the general formula (I) as defined herein, its tautomeric form, its stereoisomer, its polymorph, its solvate, and its pharmaceutically acceptable salt in combination with the usual pharmaceutically employed carriers, diluents, and the like are useful for the treatment of a disease or disorder such as cancer, inflammation or inflammatory disease or disorder, or allergic or autoimmune disease or disorder.

The present disclosure provides a pharmaceutical composition, containing the compound of the general formula (I) as defined herein, its tautomeric form, its stereoisomer, its polymorph, its solvate, and its pharmaceutically acceptable salt in combination with the usual pharmaceutically employed carriers, diluents, and the like are useful for the treatment of a disease or disorder such as ABC-DLBCL type of lymphomas, a subset of GCB-DLBCL type of lymphomas involving MALT1, MALT lymphomas, mantle cell lymphoma, marginal zone lymphoma, cutaneous T cell lymphomas, primary effusion lymphoma, pancreatic cancer, chronic lymphocytic leukemia with CARD11 mutation, Hodgkin's and Non-Hodgkin's lymphomas, or a subset of acute myelogenous leukemia involving MALT1, germ cell tumors and neoplasm involving plasma cell, brain tumors including glioblastoma, hepatic adenomas, medulloblastoma, mesothelioma, different types of melanomas and multiple myeloma, clear cell carcinoma, or adenocarcinoma of lung, breast, bladder, skin, brain, colon, stomach, cervix, ovary, uterus, prostate, liver, and kidney, psoriasis, multiple sclerosis, systemic lupus erythematosus, BENTA disease, ulcerative colitis, pancreatitis, rheumatic fever, or rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, Crohn's disease, gastritis, celiac disease, gout, organ or transplant rejection, chronic allograft rejection, acute or chronic graft-versus-host disease, Behcet's disease, uveitis, dermatitis including atopic dermatitis, dermatomyositis, inflammation of skeletal muscles leading to polymyositis, myasthenia gravis, Grave's disease, Hashimoto thyroiditis, blistering disorders, vasculitis syndromes, Hennoch-Schonlein Purpura, or immune-complex vasculitides, Sjoren's syndrome, asthma, bronchitis, or chronic obstructive pulmonary disease, cystic fibrosis, and respiratory diseases involving lungs leading to respiratory distress and failure.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is related to a compound of the general formula (I), its tautomeric form, its stereoisomer, its pharmaceutically acceptable salt, its polymorph, its solvate, its combination with suitable one or more other medicaments, its pharmaceutical composition, method of making of the compound, its use as MALT1 inhibitor, and its therapeutic utility in treating, or ameliorating various pathological conditions. The compounds are of formula (I) below:

CLAIMS

1. 1-(6-(2H-1,2,3-Triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-3-(7-(1-methoxyethyl)-2-methylthiazolo[5,4-b]pyridin-6-yl)urea or a pharmaceutically acceptable salt thereof.
- 5 2. The compound of claim 1 comprising 1-(6-(2H-1,2,3-Triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-3-(7-(1-methoxyethyl)-2-methylthiazolo[5,4-b]pyridin-6-yl)urea.
3. The compound of claim 1 comprising a stereoisomer of 1-(6-(2H-1,2,3-Triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-3-(7-(1-methoxyethyl)-2-methylthiazolo[5,4-b]pyridin-6-yl)urea or a pharmaceutically acceptable salt thereof.
- 10 4. The compound of claim 3 comprising a stereoisomer of 1-(6-(2H-1,2,3-Triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-3-(7-(1-methoxyethyl)-2-methylthiazolo[5,4-b]pyridin-6-yl)urea.
- 15 5. A racemic mixture comprising the compound of claim 1.
6. ($\pm$)-1-(6-(2H-1,2,3-Triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-3-(7-(1-methoxyethyl)-2-methylthiazolo[5,4-b]pyridin-6-yl)urea or a pharmaceutically acceptable salt thereof.
7. The compound of claim 6 comprising ($\pm$)-1-(6-(2H-1,2,3-Triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-3-(7-(1-methoxyethyl)-2-methylthiazolo[5,4-b]pyridin-6-yl)urea.
- 20 8. A racemic mixture comprising the compound of claim 6.
9. (+)-1-(6-(2H-1,2,3-Triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-3-(7-(1-methoxyethyl)-2-methylthiazolo[5,4-b]pyridin-6-yl)urea or a pharmaceutically acceptable salt thereof.
- 25 10. The compound of claim 9 comprising (+)-1-(6-(2H-1,2,3-Triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-3-(7-(1-methoxyethyl)-2-methylthiazolo[5,4-b]pyridin-6-yl)urea.
11. (-)-1-(6-(2H-1,2,3-Triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-3-(7-(1-methoxyethyl)-2-methylthiazolo[5,4-b]pyridin-6-yl)urea or a pharmaceutically acceptable salt thereof.
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12. The compound of claim 11 comprising (-)-1-(6-(2H-1,2,3-Triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-3-(7-(1-methoxyethyl)-2-methylthiazolo[5,4-b]pyridin-6-yl)urea.