PYRIMIDINE COMPOUNDS FOR USE AS MAP4K1 INHIBITORS

RELATED APPLICATIONS

This application claims the benefit of Indian Provisional Application No. 202121030204 filed on July 06, 2021; which is hereby incorporated by reference in its entirety.

TECHNICAL FIELD

The present patent application is directed to pyrimidine phospho compounds which are useful as MAP4K1 inhibitors.

BACKGROUND

Protein kinases represent a large family of proteins which play a variety of crucial roles in the regulation of a wide range of cellular processes. Such kinases include Akt, Axl, Aurora A, Aurora B, DYRK2, EPHAa2, FGFR3, FLT-3, VEGFr3, IGFLr, IKK2, JNK3, VEGFr2, MEK1, MET, P70s6K, Plk1, RSK1, Src, TrkA, Zap70, cKit, bRaf, EGFR, Jak2, PI3K, NPM-Alk, c-Abl, BTK, FAK, PDGFR, TAK1, LimK, Flt1, PDK1, Erk and RON. Inhibition of various protein kinases, especially selective inhibition, has become an important strategy in treating many diseases and disorders.

MAP4K1 is a serine/threonine kinase of the Ste20 family. MAP4K enzymes (MAP kinase kinases) are generally involved at the highest level of a largely linear kinase activation pathway. A MAP4K will phosphorylate and activate a particular substrate which is a MAP3K (a MAP kinase kinase). A MAP3K in turn phosphorylates and activates a MAP2K (a MAP kinase kinase). A MAP2K in turn phosphorylates and activates a MAPK (MAP kinase). The MAP kinase is the final effector of the pathway and it in turn phosphorylates a substrate to control key cellular processes such as cell proliferation, cell differentiation, gene expression, transcription regulation, and apoptosis. The substrate of MAPK is generally a nuclear protein, such as nuclear factor kappa-B (NF-κB). Activation of the MAPK by its phosphorylation by an MAP2K results in translocation of this final enzyme in the cascade into the nucleus.

MAP4K1, also known as HPK1, is primarily expressed in the immune system's Tcells and B cells, which are critical in regulation of the immune system. Overstimulation of T cell and B cell activation pathways can result in auto-immune diseases, while understimulation of these pathways can result in immune dysfunction, susceptibility to viral and bacterial infection and increased susceptibility to cancer. MAP4K1 is activated by its interaction with activated T cell receptors (TCRs) and B cell receptors (BCRs), so MAP4K1 activation serves to convey the

inhibitor of tyrosine kinases. Lestaurtinib is primarily an inhibitor of the FLT, JAK and TRK family tyrosine kinases. Crizotinib is primarily an inhibitor of the c-met and ALK tyrosine kinases. Foretinib was under study as an inhibitor of the c-Met and VEGFR tyrosine kinases. Dovitinib is primarily an inhibitor of the FGFR receptor tyrosine kinase. KW-2449 is an experimental inhibitor primarily of the FLT3 tyrosine kinase.

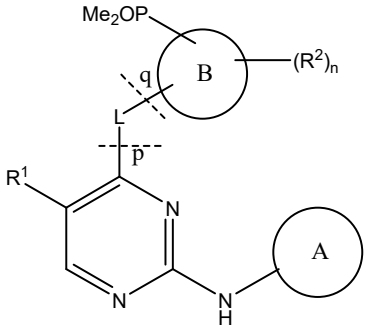
Sunitinib inhibits MAP4K1 at nanomolar concentrations, but it is a broad-spectrum receptor tyrosine kinase inhibitor. Treating T-cells with sunitinib results in enhanced cytokine product similar to that observed with HPK1 –/– T cells, which suggests that in T cells a selective MAP4K1 inhibitor could produce the same enhanced immune response phenotype.

Currently, there is a largely unmet need for an effective way of treating disease and disorders associated disrupted protein kinase signaling. Autoimmune diseases, inflammatory diseases, neurological and neurodegenerative diseases, cancer, cardiovascular diseases, allergies and asthma, are all diseases and disorder which can be affected by dysfunctional protein kinase signaling. Improved therapeutic compounds, compositions and methods for the treatment for these disease and disorders are urgently required. MAP4K1 inhibition is an especially attractive target for cancer immunotherapy.

The major challenge currently faced in the field is the lack of MAP4K1 specific inhibitors. The present disclosure provides novel, highly effective small-molecule inhibitors of MAP4K1.

SUMMARY

In one aspect, the present disclosure relates to compound of formula (I)



(I)

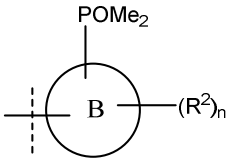
or a tautomer thereof, stereoisomer thereof, or a pharmaceutically acceptable salt thereof, wherein

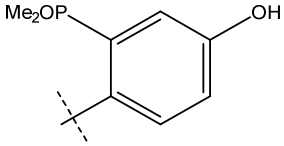
R^1 is selected from chloro and $–CONH_2$;

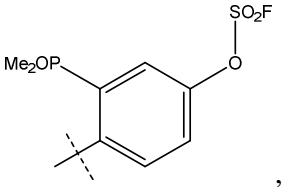
The compounds of formula (I) may involve one or more embodiments. It is to be understood that the embodiments below are illustrative of the present disclosure and are not intended to limit the claims to the specific embodiments exemplified. It is also to be understood that the embodiments defined herein may be used independently or in conjunction with any definition, any other embodiment defined herein. Thus the present disclosure contemplates all possible combinations and permutations of the various independently described embodiments. For example, the present disclosure provides compounds of formula (I) as defined above wherein R^1 is chloro (according to an embodiment defined below), R^1 is $–CONH_2$ (according to another embodiment defined below) and R^c is methyl (according to yet another embodiment defined below).

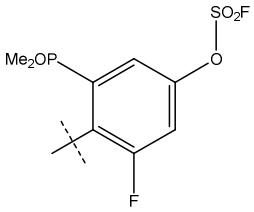
According to one embodiment, specifically provided are compounds of formula (I), in which R^1 is chloro.

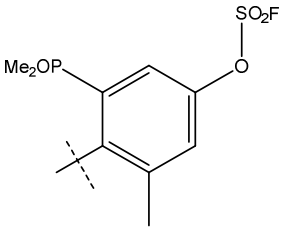
According to another embodiment, specifically provided are compounds of formula (I), in which R^1 is $-CONH_2$.

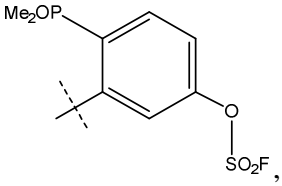
According to yet another embodiment, specifically provided are compounds of formula (I), in which 

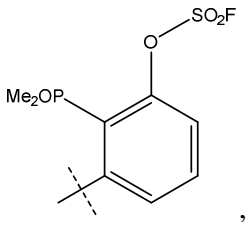
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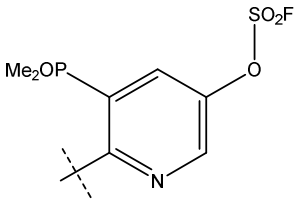
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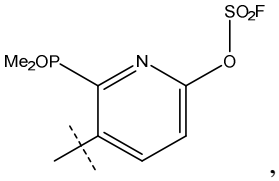
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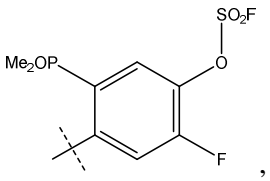
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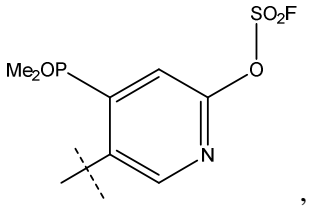
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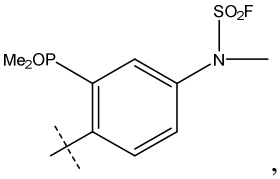
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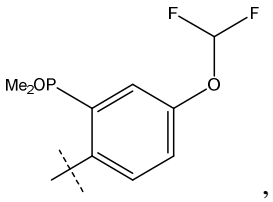
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According to an embodiment, specifically provided are compounds of formula (I) with an IC_{50} value of less than 500 nM, preferably less than 100 nM, more preferably less than 50 nM, with respect to MAP4K1 inhibition.

Compounds of the present disclosure include the compounds in Examples 1-61. It should be understood that the formula (I) structurally encompasses all geometrical isomers, stereoisomers, enantiomers and diastereomers, *N*-oxides, and pharmaceutically acceptable salts that may be contemplated from the chemical structure of the genera described herein.

The present application also provides a pharmaceutical composition that includes at least one compound 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. The compounds described herein 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 tablet, capsule, sachet or other container.

Pharmaceutical compositions comprising Compounds of the present disclosure may be prepared using conventional diluents or excipients and techniques known in the art.

DETAILED DESCRIPTION

Definitions:

The terms "halogen" or "halo" means fluorine (fluoro), chlorine (chloro), bromine (bromo), or iodine (iodo).

The term "alkyl" refers to a hydrocarbon chain radical that includes solely carbon and hydrogen atoms in the backbone, containing no unsaturation, having from one to eight carbon atoms (i.e. $C_{1\text{-}8}$alkyl), and which is attached to the rest of the molecule by a single bond, such as, but not limited to, methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, n-pentyl, and 1,1-dimethylethyl (t-butyl). The term "$C_{1\text{-}6}$alkyl" refers to an alkyl chain having 1 to 6 carbon atoms. The term "$C_{1\text{-}4}$alkyl" refers to an alkyl chain having 1 to 4 carbon atoms. Unless set forth or recited to the contrary, all alkyl groups described or claimed herein may be straight chain or branched.

The term "haloalkyl" refers to at least one halo group (selected from F, Cl, Br or I), linked to an alkyl group as defined above (i.e. halo$C_{1\text{-}8}$alkyl). Examples of such haloalkyl moiety include, but are not limited to, trifluoromethyl, difluoromethyl and fluoromethyl groups. The term "halo$C_{1\text{-}4}$alkyl" refers to at least one halo group linked an alkyl chain having 1 to 4

disease and its severity and the age, weight, physical condition and responsiveness of the subject to be treated.

The compounds of formula (I) may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of formula (I) as well as mixtures thereof, including racemic mixtures, form part of the present disclosure. In addition, the present disclosure embraces all geometric and positional isomers. Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolysing) the individual diastereomers to the corresponding pure enantiomers. Enantiomers can also be separated by use of chiral HPLC column. The chiral centres of the present disclosure can have the S or R configuration as defined by the IUPAC 1974.

The terms "salt" or "solvate", and the like, is intended to equally apply to the salt, solvate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers or racemates of the inventive compounds.

PHARMACEUTICAL COMPOSITIONS

The compounds of the present disclosure 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 present disclosure. The pharmaceutical compositions described herein comprise one or more compounds described herein and one or more pharmaceutically acceptable excipients.

METHODS OF TREATMENT

The compounds of Formula (I) as described herein are highly effective inhibitors of the MAP4K1 kinase, producing inhibition at nanomolar concentrations. MAP4K1 inhibitors according to the present disclosure are therefore useful for treatment and prophylaxis of diseases associated with protein kinase signaling dysfunction. Accordingly, without being bound by any theory, it is believed that inhibition of MAP4K1 could, for example, reverse or prevent the cellular dysfunction associated with perturbations of the JNK signaling pathway, especially in T and B cells. Therefore, administration of a MAP4K1 inhibitor as described

herein could provide a potential means to regulate MAPK signal transduction pathways, especially the JNK pathway, and by extension provide a treatment for a variety of diseases and disorders including autoimmune, neurodegenerative, neurological, inflammatory, hyperproliferative, and cardiovascular diseases and disorders.

In addition, without being bound by theory, selective MAP4K1 inhibition, as provided by the Compounds of the present disclosure, may provide a novel means of cancer treatment. Traditional signal transduction strategies relate to interference with the pathways that promote tumor cell proliferation or metastasis. The present disclosure provides instead a means of enhancing the activity and effectiveness of the body's T cells, for example, to overcome the immunosuppressive strategies used by many cancers. The U.S. Food and Drug Administration (FDA) has recently approved some monoclonal antibody-based treatments that achieve the same result by interfering with T-cell surface receptors which promote inhibition of TCR activity (e.g., anti-CTLA-4 and anti-PD-1 antibodies, marketed as Ipilimumab and Pembrolizumab, respectively). The success of the treatments demonstrates proof of the concept that cancer can be effectively treated by interfering with pathways which inhibit TCR signaling. Targeting these pathways using a small molecule inhibitor of MAP4K1 should produce improved results using more patient-friendly administration techniques.

Therefore, in the third aspect, the present disclosure provides a method for the treatment or prophylaxis of a disease or disorder which may be ameliorated by modulating (e.g., inhibiting) MAP4K1-dependent signaling pathways, including the JNK pathway, e.g., autoimmune, neurodegenerative, neurological, inflammatory, hyperproliferative, and cardiovascular diseases and disorders, comprising administering to a patient in need thereof an effective amount of the compound of Formula (I) as described herein, in free or pharmaceutically acceptable salt form.

In particular embodiments, administration of the compounds of the present disclosure results in enhanced T cell receptor (TCR) signaling, such as resulting in an enhanced T cell-mediated immune response (e.g., increased T cell cytokine production).

In other particular embodiments, administration of the compounds of the present disclosure results in increased T cell resistance to PGE2-mediated T cell suppression.

In certain embodiments, the disease or disorder to be treated may also relate to impaired MAP4K1-dependent signaling. Impaired MAP4K1 signaling can lead to reduced immune cell, e.g. T and B cell, function which can permit or enhance the escape of nascent cancer cells from immune surveillance. Restoration of T and B cell function via treatment with a MAP4K1-inhibitor can therefore promote the clearance of carcinogenic and pre-carcinogenic cells from

the body. Thus, in a particular embodiment, the invention provides a method for the treatment or prevention of hyperproliferative diseases, such as cancer.

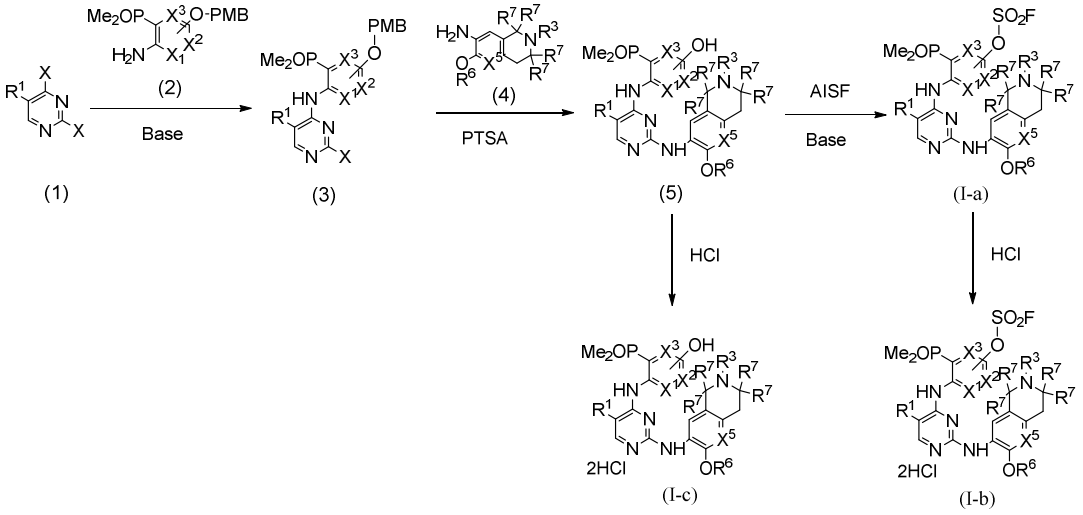
GENERAL METHODS OF PREPARATION

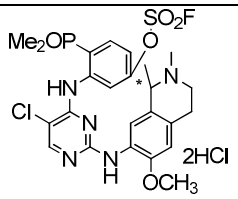
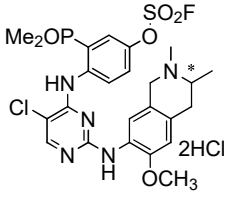
The compounds, described herein, including those of general formula (I), intermediates and specific examples are prepared through the synthetic methods as depicted in synthetic schemes 1-15. Furthermore, in the following schemes, where specific acids, bases, reagents, coupling reagents, solvents, etc. are mentioned, it is understood that other suitable acids, bases, reagents, coupling reagents, solvents etc. may be used and are included within the scope of the present disclosure. The modifications to reaction conditions, for example, temperature, duration of the reaction or combinations thereof, are envisioned as part of the present disclosure. The compounds obtained using the general reaction sequences may be of insufficient purity. These compounds can be purified using any of the methods for purification of organic compounds known to persons skilled in the art, for example, crystallization or silica gel or alumina column chromatography using different solvents in suitable ratios. All possible geometrical isomers and stereoisomers are envisioned within the scope of the present disclosure.

General schemes

A general approach for the preparation of compounds of the formulae (I(a-c)) (wherein X^1, X^2, X^3 are CH or N; X^5 is CH or N; R^3 is hydrogen, C_{1-8}alkyl, deuterated C_{1-8}alkyl, haloC_{1-8}alkyl or 3-15 membered heterocyclyl; R^6 is C_{1-8}alkyl, deuterated C_{1-8}alkyl or haloC_{1-8}alkyl; R^7 is hydrogen, oxo, deuterium or C_{1-8}alkyl and R^1 is as defined in the general description) is depicted in synthetic scheme 1.

Synthetic Scheme 1



Example No.	Structure	Method and Intermediate	Chemical Name and Analytical data
			DMSO-d_6) δ 1.41-1.57 (m, 3H), 1.85 (d, J = 13.6 Hz, 6H), 2.76-2.87 (m, 3H), 3.03-3.10 (m, 1H), 3.13-3.17 (m, 1H), 3.31 - 3.57 (m, 2H), 3.79 (s, 3H), 4.39 - 4.55 (m, 1H), 6.94 (d, J = 4.8 Hz, 1H), 7.37 (d, J = 7.2 Hz, 1H), 7.58 (s, 1H), 7.81-7.86 (m, 1H), 8.24 (s, 1H), 8.64 (brs, 1H), 8.82 (brs, 1H), 11.84 (brs , 1H); ESI-MS (*m/z*) 584.2 $(M+H)^+$.
Example 32	 Isomer 2	Method A/A1 A5/B15	3-((5-Chloro-2-((6-methoxy-1, 2-dimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl) amino)pyrimidin-4-yl)amino)-4-(dimethylphosphoryl)phenyl sulfofluoridate dihydrochloride (Isomer 2); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.41-1.57 (m, 3H), 1.85 (d, J = 13.6 Hz, 6H), 2.76-2.87 (m, 3H), 3.03-3.10 (m, 1H), 3.13-3.17 (m, 1H), 3.31 - 3.57 (m, 2H), 3.79 (s, 3H), 4.39 - 4.55 (m, 1H), 6.94 (d, J = 4.8 Hz, 1H), 7.37 (d, J = 7.2 Hz, 1H), 7.58 (s, 1H), 7.81-7.86 (m, 1H), 8.24 (s, 1H), 8.64 (brs, 1H), 8.82 (brs, 1H), 11.84 (brs , 1H); ESI-MS (*m/z*) 584.2 $(M+H)^+$.
Example 33		Method A/A1 A1/B17	4-((5-Chloro-2-((6-methoxy-2, 3-dimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl) amino)pyrimidin-4-yl)amino)-3-

Tumor growth inhibition (TGI) at day 24, is shown in figure 1 for Example 2. Tumor growth inhibition was observed in response to treatment with Example 2 with 10 mg/kg and 50 mg/kg QD by 40% and 61% respectively when compared with vehicle group.

Tumor growth inhibition (TGI) at day 25, is shown in figure 2 for Example 30. Tumor growth inhibition was observed in response to treatment with Example 30 with 10 mg/kg and 50 mg/kg QD by 37% and 62% respectively when compared with vehicle group.

Although the present disclosure herein has been described with reference to particular embodiments, it is to be understood that these embodiments are merely illustrative of the principles and applications of the present disclosure. It is therefore to be understood that numerous modifications may be made to the illustrative embodiments and that other arrangements may be devised without departing from the spirit and scope of the present disclosure as described above.

All publications and patent applications cited in this application are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated herein by reference.