

**TRICYCLIC COMPOUNDS, COMPOSITIONS AND MEDICINAL
APPLICATIONS THEREOF**

FIELD OF THE INVENTION

5 **[001]** The present disclosure relates a series of tricyclic compounds, their
tautomers, polymorphs, stereoisomers, prodrugs, solvates, pharmaceutically
acceptable salts, pharmaceutical compositions containing them and methods of
treating conditions and diseases that are mediated by adenosine receptor (AR)
activity. These compounds are useful in the treatment, prevention or suppression of
10 diseases and disorders that may be susceptible to improvement by antagonism of the
adenosine receptor. The disclosure also relates to the process of preparation of the
tricyclic compounds, and to pharmaceutical compositions containing them.

BACKGROUND OF INVENTION

15 **[002]** Adenosine is an endogenous modulator of a wide range of physiological
functions and is implicated in several pathologies. Recent advances in molecular
biology coupled with several pharmacological studies have lead to identification of
at least four subtypes of adenosine receptors, A₁, A_{2A}, A_{2B} and A₃. The A₁ and A₃
receptors down-regulate cellular cAMP levels through their coupling to G protein,
which inhibit adenylate cyclase. In contrast, A_{2A} and A_{2B} receptors couple to G
20 protein that activate adenylate cyclase and increase intracellular levels of cAMP.

[003] Advances in understanding the role of adenosine and its receptors in
physiology and pathophysiology as well as new developments in medicinal
chemistry of these receptors have identified potential therapeutic areas for drug
development. With the combination of pharmacological data using selective ligands
25 and genetically modified mice, important progress has been made towards
understanding of the role of adenosine receptors (Ars) in a variety of diseases, such
as inflammatory conditions, sepsis, heart attack, ischemia-reperfusion injury,
vascular injury, spinal cord injury, chronic obstructive pulmonary disease (COPD),
asthma, diabetes, obesity, inflammatory bowel disease, retinopathy, and Parkinson's
30 Disease (PD).

[004] In the central nervous system, A_{2A} antagonists can have antidepressant properties and stimulate cognitive functions. Epidemiological evidence shows a protective role for caffeine in Parkinson's disease. Moreover, A_{2A} receptor density is found to be very high in the basal ganglia which regulate motor control function.

5 Hence, selective A_{2A} antagonists can improve motor impairment due to neurodegenerative diseases, such as, Parkinson's disease (Trends Pharmacol. Sci. 1997, 18, 338-344), senile dementia as in Alzheimer's disease, psychoses, stroke and be potentially effective in the treatment of cerebral ischaemia (Life Sci. 1994, 55, 61-65). A_{2A} antagonists may also be employed for the treatment or management of
10 attention related disorders such as attention deficit disorder and attention deficit hyperactivity disorder, extra pyramidal syndrome, e.g., dystonia, akathisia, pseudoparkinsonism and tardive dyskinesia, and disorders of abnormal movement such as restless leg syndrome and periodic limb movement in sleep. Several of these indications have been disclosed in patent applications (eg. WO 02/055083, WO
15 05/044245 and WO 06/132275). Adenosine A_{2A} antagonists could also be useful in the treatment of amyotrophic lateral sclerosis, cirrhosis, and fibrosis and fatty liver (US2007037033, WO 01/058241). A_{2A} receptor antagonists are also useful for the mitigation of addictive behavior (WO 06/009698) and for the treatment and prevention of dermal fibrosis in diseases such as scleroderma (Arthritis &
20 Rheumatism, 2006; 54(8), 2632-2642).

[005] Parkinson's disease (PD) is a progressive, incurable disorder with no definite preventive treatment, although drugs are available to alleviate the symptoms and/or slow down the progress of the disease. Among the various strategies, A_{2A} AR blockers are considered a potential approach to treatment of the disease. Within the
25 brain A_{2A} ARs are richly expressed in the striatum, nucleus accumbens, and olfactory tubercle. Co-expression of A_{2A} with D2 dopamine receptors has been reported in the GABAergic striatopallidal neurons where adenosine and dopamine agonists exert antagonistic effects in the regulation of locomotor activity. Activation of A_{2A} ARs in striatopallidal neurons decreases the affinity of D2 receptors for dopamine,
30 antagonizing the effects of D2 receptors. The negative interaction between A_{2A} and D2 receptors is at the basis of the use of A_{2A} antagonists as a novel therapeutic

approach in the treatment of PD (Pharmacol. Ther. 2005, 105, 267). The recent discovery that the A_{2A} can form functional heteromeric receptor complexes with other G protein-coupled receptors such as D2 receptors and the mGlu5 receptors has also suggested new opportunities for the potential of A_{2A} antagonists in PD (J. Mol. Neurosci. 2005, 26, 209).

[006] Adenosine signaling is known to serve apoptotic, angiogenic and pro-inflammatory functions and might be relevant to the pathogenesis of asthma and chronic obstructive pulmonary disease (Trends in Pharmacol. Sci., 2003, 24, 8). Extracellular adenosine acts as a local modulator with a generally cytoprotective function in the body. Its effects on tissue protection and repair fall into four categories: increasing the ratio of oxygen supply to demand; protecting against ischaemic damage by cell conditioning; triggering anti-inflammatory responses; and the promotion of angiogenesis.

[007] The A_{2B} adenosine receptor subtype (I. Pharmacol. Rev. 1997, 49, 381-402) has been identified in a variety of human and murine tissues and is involved in the regulation of vascular tone, smooth muscle growth, angiogenesis, hepatic glucose production, bowel movement, intestinal secretion, and mast cell degranulation.

[008] A_{2B} receptors have been implicated in mast cell activation and asthma, control of vascular tone, cardiac myocyte contractility, cell growth and gene expression, vasodilation, regulation of cell growth, intestinal function, and modulation of neurosecretion (Pharmacol. Rev., 2003, 49, 4).

[009] A_{2B} receptors modulate mast cell function. Adenosine activates adenylate cyclase and protein kinase C and potentiates stimulated mediator release in mouse bone marrow derived mast cells. Activation of A_{2B} receptors in HMC-1 augments IL-8 release and potentiates PMA-induced secretion of IL-8. Thus, adenosine would contribute to the asthmatic response by acting on the mast cell to enhance the release of proinflammatory mediators. (Pulmonary Pharmacology & Therapeutics 1999, 12, 111-114). In COPD, transformation of pulmonary fibroblasts into myofibroblasts is considered a major mechanism. Activation of the A_{2B} AR is involved in this process. Selective A_{2B} antagonists are expected to have beneficial effect on pulmonary fibrosis (Curr. Drug Targets, 2006, 7, 699-706; Am. J. Respir. Cell. Mol. Biol., 2005,

32, 228). A_{2B} antagonists can be used as wound healing agents. Activation of the A_{2B} AR promotes angiogenesis by increasing the release of angiogenic factors and A_{2B} antagonists are useful to block angiogenesis (Circ. Res., 2002, 90, 531-538). A_{2B} AR may be involved in the inhibition cardiac fibroblast (CF) proliferation (Am.J. Physiol. Heart Circ. Physiol., 2004, 287, H2478-H2486). Adenosine stimulates Cl-secretion in the intestinal epithelia pointing towards a possible treatment for cystic fibrosis patients with CFTR mutation (Am. J. Respir. Cell Mol. Biol., 2008, 39, 190-197). High affinity A_{2B} antagonists are effective in hot plate model suggestive of the role of A_{2B} in nociception and can be used as potential analgesic agents (The J. of Pharmacol. and Exp. Ther., 2004, 308, 358-366).

[0010] A_{2B} receptor is involved in release of IL-6. Increasing evidence suggests that IL-6 plays a role in Alzheimer's disease in the context of inflammatory process associated with disease. Hence A_{2B} receptor antagonist might be useful for Alzheimer's disease.

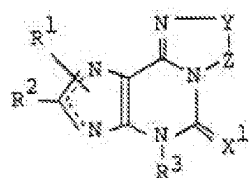
[0011] The A_{2B} ARs are involved in the stimulation of nitric oxide production during Na⁺-linked glucose or glutamine absorption. They are involved in glucose production in hepatocytes upon agonist stimulation. A_{2B}-receptor antagonists showed an anti-diabetic potential mainly by increasing plasma insulin levels under conditions when the adenosine tonus was elevated in-vivo and increased insulin release in-vitro (J Pharm. Pharmacol. 2006 Dec; 58(12);1639-45). Thus, A_{2B} antagonists may serve as a novel target for the treatment of this metabolic disease.

[0012] It has been demonstrated that adenosine activation of the A_{2B} adenosine receptor increase cAMP accumulation, cell proliferation and VEGF expression in human retinal endothelial cells. Activation of A_{2B}AdoR increased vascular endothelial cell growth factor mRNA and protein expression in human retinal endothelial cells. Adenosine also has a synergistic effect with VEGF on retinal endothelial cell proliferation and capillary morphogenesis in vitro. Such activity is necessary in healing wounds, but the hyperproliferation of endothelial cells promotes diabetic retinopathy. Also, an undesirable increase in blood vessels occurs in neoplasia. Accordingly, inhibition of binding of adenosine to A_{2B} receptors in the

endothelium will alleviate or prevent hypervasculation, thus preventing retinopathy and inhibiting tumor formation.

[0013] Adenosine generation in tumor microenvironment is an active metabolic mechanism used by cancer cells to avoid anti-tumor immunosurveillance and increase metastasis. Ectonucleotidase CD73 and CD39 (highly expressed on tumor cells and stromal cells) convert ATP released by dying tumor cells to adenosine. A_{2B} receptors are expressed at low levels on multiple cell types under normal conditions, but significantly upregulated under hypoxic conditions that prevail in the tumor microenvironment. Activation of A_{2B} receptors promotes angiogenesis and causes T cell and myeloid derived suppressor cell (MDSC) mediated immunosuppression in the tumor microenvironment. A_{2B} antagonists could induce anti-tumoral responses in multiple types of cancer when used as stand alone or in combination with existing immunotherapies or radiotherapy or chemotherapy. Cancers that could benefit from A_{2B} antagonist therapy include melanoma, triple negative breast cancer, colon cancer, colorectal cancer, lung cancer, prostate cancer, renal cell cancer, non-small cell lung cancer, bladder cancer, cervical, vulvar or anal cancer, esophageal cancer, metastatic head and neck cancer, liver cancer, lymphoma, multiple myeloma, ovarian cancer, pancreatic cancer, acute myeloid leukemia, Kaposi sarcoma.

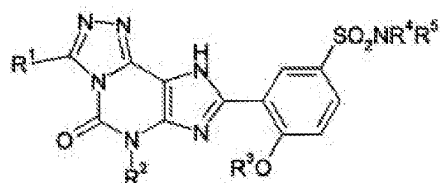
[0014] EP417790 discloses compounds represented by the formula:



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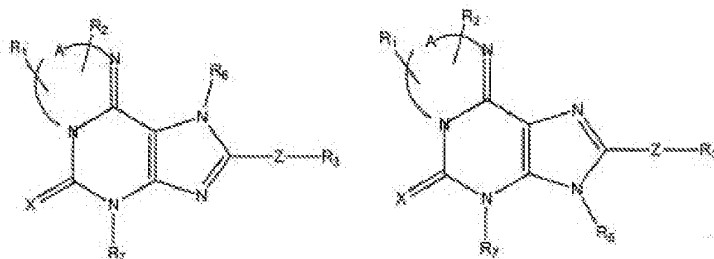
wherein each symbol is as defined in the specification, useful as bronchodilators, diuretics, renal protectants, and antiemetic agents.

[0015] WO200107441 discloses compounds represented by the formula:



wherein each symbol is as defined in the specification, useful as PDE 5 inhibitors.

[0016] WO200244182 and WO200322284 disclose compounds represented by the formula:



5 wherein each symbol is as defined in the specification, useful as Adenosine A₁ receptor antagonist.

[0017] While many of these biological effects of adenosine are necessary to maintain normal tissue homeostasis, under certain physiological changes it is desirable to modulate its effects. For example, the binding of A_{2B} receptors stimulates
 10 angiogenesis by promoting the growth of endothelial cells. Such activity is necessary in healing wounds, but the hyperproliferation of endothelial cells promotes diabetic retinopathy. Also, an undesirable increase in blood vessels occurs in neoplasia. Accordingly, inhibition of the binding of adenosine to A_{2B} receptors in the endothelium will alleviate or prevent hypervasculation, thus preventing retinopathy
 15 and inhibiting tumor formation.

[0018] A_{2B} receptors are found in the colon in the basolateral domains of intestinal epithelial cells, and when acted upon by the appropriate ligand act to increase chloride secretion, thus causing diarrhea, which is a common and potentially fatal complication of infectious diseases such as cholera and typhus. A_{2B} antagonists can
 20 therefore be used to block intestinal chloride secretion and are thus useful in the treatment of inflammatory gastrointestinal tract disorders, including diarrhea. Another adverse biological effect of adenosine acting at the A_{2B} receptor is the overstimulation of cerebral IL-6, a cytokine associated with dementias and Alzheimer's disease.

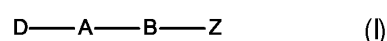
25 **[0019]** Accordingly, it is desired to provide compounds that are potent A_{2A}/A_{2B} dual antagonists (i.e., compounds that inhibit the A_{2A}/A_{2B} adenosine receptor), fully or

partially selective for the A_{2A}/A_{2B} receptor, useful in the treatment of various disease states related to modulation of the A_{2A}/A_{2B} receptor, for example cancer.

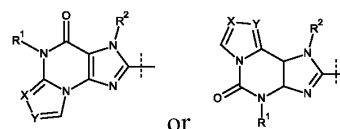
SUMMARY OF THE INVENTION

[0020] In an aspect of the present disclosure, there is provided a compound of

- 5 Formula I, or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, prodrugs, racemic mixtures, optically active forms and pharmaceutically active derivatives thereof,



wherein



- 10 D represents a tricyclic ring system selected from
 wherein R¹ is selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl;
 R² is selected from hydrogen, alkyl, alkenyl, alkynyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl;
 15 wherein alkyl, alkenyl, alkynyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl are unsubstituted or substituted independently with alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, monoalkylamino, dialkylamino, arylamino, cycloalkylamino, heteroarylamino, heterocyclylamino, aminocarbonyl,
 20 alkoxy carbonylamino, azido, cyano, halogen, hydroxy, hydroxyalkyl, keto, thiocarbonyl, carboxy, alkylcarboxy, carboxyalkyl, carboxyalkyloxy, alkylcarboxyalkyloxy, -SO₃H, aryl, aryloxy, cycloalkyloxy, heteroaryl, aminocarbonylamino, heteroaryloxy, heterocyclyl, heterocycliloxy, hydroxyamino, alkoxyamino, nitro, S(O)₂NR^cR^c, -NR^cS(O)₂R^c or -S(O)_pR^d;
 25 wherein each substituent is unsubstituted or substituted with 1, 2, or 3 substituents independently selected from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxyd, alkoxy, halogen, haloalkyl, haloalkoxy, amino, substituted amino, cyano or -S(O)_pR^d;

X and Y are independently selected from CR' or N, wherein R' is selected from hydrogen, halogen, alkyl and haloalkyl;

A is selected from an optionally substituted arylene or an optionally substituted heteroarylene;

- 5 B is selected from a bond, (C₁-C₆)alkylene, (C₂-C₆)alkenylene or (C₂-C₆)alkynylene group, wherein 1 to 4 methylene groups are optionally replaced by groups independently selected from O, -S(O)_p-, -N(R^b)-, or -C(O)-;
- wherein alkylene, alkenylene, and alkynylene are unsubstituted or substituted independently with alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl,
- 10 acylamino, acyloxy, amino, monoalkylamino, dialkylamino, arylamino, cycloalkylamino, heteroarylamino, heterocyclylamino, aminocarbonyl, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, hydroxyalkyl, keto, thiocarbonyl, carboxy, alkylcarboxy, carboxyalkyl, carboxyalkyloxy, alkylcarboxyalkyloxy -SO₃H, aryl, aryloxy, cycloalkyloxy, heteroaryl,
- 15 aminocarbonylamino, heteroaryloxy, heterocyclyl, heterocycliloxy, hydroxyamino, alkoxyamino, nitro, S(O)₂NR^cR^c, -NR^cS(O)₂R^c or -S(O)_pR^d;
- Z is selected from hydrogen, heterocyclyl, cycloalkyl, aryl or heteroaryl;
- wherein heterocyclyl, cycloalkyl, aryl and heteroaryl are unsubstituted or substituted independently with alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl,
- 20 cycloalkenyl, acyl, acylamino, acyloxy, amino, monoalkylamino, dialkylamino, arylamino, cycloalkylamino, heteroarylamino, heterocyclylamino, aminocarbonyl, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, hydroxyalkyl, keto, thiocarbonyl, carboxy, alkylcarboxy, carboxyalkyl, carboxyalkyloxy, alkylcarboxyalkyloxy -SO₃H, aryl, arylalkyl, aryloxy, cycloalkyloxy, heteroaryl,
- 25 heteroarylalkyl, aminocarbonylamino, heteroaryloxy, heterocyclyl, heterocyclylalkyl, heterocycliloxy, hydroxyamino, alkoxyamino, nitro, -S(O)₂NR^bR^b, -NR^bS(O)₂R^b or -S(O)_pR^d;
- wherein each substituent is unsubstituted or substituted with 1, 2, or 3 substituents independently selected from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy,
- 30 alkoxy, alkoxyalkoxy, alkoxyalkyl, halogen, haloalkyl, haloalkoxy, amino, substituted amino, cyano or -S(O)_pR^d;

R^a is selected from hydrogen, or alkyl;

R^b is selected from hydrogen, alkyl, acyl, carboxyalkyl, carbonylamino, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, or heterocyclylalkyl;

5 R^c is selected from hydrogen, alkyl, aryl, heteroaryl, or heterocyclyl;

R^d is selected from alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl; and

p is 0, 1, or 2.

[0021] In an aspect of the present disclosure there is provided a method of using the pharmaceutical composition of the present disclosure comprising a compound of
10 Formula I and their pharmaceutically acceptable salt, analog, tautomeric form, stereoisomer, geometrical isomer, polymorph, hydrate, solvate, metabolite, and prodrug thereof, in the treatment of a disease or condition in a mammal that is amenable to treatment with an A_{2A}/A_{2B} receptor antagonist, the method comprising: administering to a mammal in need thereof a therapeutically effective dose of the
15 pharmaceutical composition of the present disclosure.

[0022] In an aspect of the present disclosure there is provided a method of treatment of a disorder or condition ameliorated by antagonizing the A_{2A}/A_{2B} receptor, the method comprising: administering an effective amount of the pharmaceutical composition of the present disclosure comprising a compound of Formula I and their
20 pharmaceutically acceptable salts, analog, tautomeric form, stereoisomer, geometrical isomer, polymorph, hydrate, solvate, metabolite, and prodrug thereof, to a patient in need of such treatment.

[0023] In an aspect of the present disclosure there is provided use of the pharmaceutical composition of the present disclosure comprising compound of
25 Formula I and their pharmaceutically acceptable salt, analog, tautomeric form, stereoisomer, geometrical isomer, polymorph, hydrate, solvate, metabolite, and prodrug thereof, for the preparation of a medicament for the treatment of a condition or disorder selected from prostate cancer, rectal cancer, renal cancer, ovarian cancer, endometrial cancer, thyroid cancer, pancreatic cancer, breast cancer, colon cancer,
30 bladder cancer, brain cancer, glial cancer, melanoma cancer, pineal gland cancer, or lung cancer.

[0024] In an aspect of the present disclosure, there is provided a process of preparation of the compound of Formula I.

[0025] These and other features, aspects, and advantages of the present subject matter will become better understood with reference to the following description.

- 5 This summary is provided to introduce a selection of concepts in a simplified form. This summary is not intended to identify key features or essential features of the disclosure, nor is it intended to be used to limit the scope of the subject matter.

DETAILED DESCRIPTION

- 10 [0026] Those skilled in the art will be aware that the present disclosure is subject to variations and modifications other than those specifically described. It is to be understood that the present disclosure includes all such variations and modifications. The disclosure also includes all such steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any or more of such steps or features.

Definitions

- 15 [0027] For convenience, before further description of the present disclosure, certain terms employed in the specification, and examples are collected here. These definitions should be read in the light of the remainder of the disclosure and understood as by a person of skill in the art. The terms used herein have the meanings
20 recognized and known to those of skill in the art, however, for convenience and completeness, particular terms and their meanings are set forth below.

[0028] The articles “a”, “an” and “the” are used to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article.

- 25 [0029] Throughout the description and the claims which follow, unless the context requires otherwise, the word “comprise”, and variations such as “comprises” and “comprising”, will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

- 30 [0030] The term “including” is used to mean “including but not limited to”. “Including” and “including but not limited to” are used interchangeably.

[0031] In the structural formulae given herein and throughout the present disclosure, the following terms have been indicated meaning, unless specifically stated otherwise.

[0032] The term "optionally substituted" as used herein means that the group in question is either unsubstituted or substituted with one or more of the substituents specified. When the group in question is substituted with more than one substituent, the substituent may be same or different.

[0033] The term "alkyl" refers to a monoradical branched or unbranched saturated hydrocarbon chain having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 carbon atoms, preferably 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms, more preferably 1, 2, 3, 4, 5 or 6 carbon atoms. This term is exemplified by groups such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-hexyl, n-decyl, tetradecyl, and the like.

[0034] The term "alkylene" refers to a diradical of a branched or unbranched saturated hydrocarbon chain, having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 carbon atoms, preferably 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms, more preferably 1, 2, 3, 4, 5 or 6 carbon atoms. This term is exemplified by groups such as methylene (-CH₂-), ethylene (-CH₂CH₂-), the propylene isomers (e.g., -CH₂CH₂CH₂- and -CH(CH₃)CH₂-) and the like.

[0035] The term "substituted alkyl" or "substituted alkylene" refers to:

- 1) an alkyl group or alkylene group as defined above, having 1, 2, 3, 4 or 5 substituents, preferably 1, 2 or 3 substituents, selected from the group consisting of alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, monoalkylamino, dialkylamino, arylamino, heteroarylamino, aminocarbonyl, alkoxy-carbonylamino, azido, cyano, halogen, hydroxy, hydroxyalkyl, keto, thiocarbonyl, carboxy, carboxyalkyl, -SO₃H, aryl, aryloxy, heteroaryl, aminocarbonylamino, heteroaryloxy, heterocyclyl, heterocyclyloxy, hydroxyamino, alkoxyamino, nitro, -S(O)₂NR^a, -NR^aS(O)₂R^a and -S(O)_pR^b, where each R^a is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl; heterocyclyloxy where R^b is hydrogen, alkyl, aryl, heteroaryl or

heterocyclyl. Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1, 2, or 3 substituents selected from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF₃, amino, substituted amino, cyano, and -S(O)_pR^c, where R^c is alkyl, aryl, or heteroaryl and p is 0, 1 or 2;

5 or 2) an alkyl group or alkylene group as defined above that is interrupted by 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 atoms independently selected from oxygen, sulfur and NR^d, where R^d is selected from hydrogen, alkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl and heterocyclyl, carbonylalkyl, carboxyester, carboxyamide and sulfonyl. All

10 substituents may be optionally further substituted by alkyl, alkoxy, halogen, CF₃, amino, substituted amino, cyano, or -S(O)_pR^c, in which R^c is alkyl, aryl, or heteroaryl and p is 0, 1, or 2;

or 3) an alkyl or alkylene as defined above that has 1, 2, 3, 4 or 5 substituents as defined above, as well as interrupted by 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 atoms as defined

15 above.

[0036] The term "alkenyl" refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 carbon atoms, more preferably 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms and even more preferably 2, 3, 4, 5 or 6 carbon atoms and

20 having 1, 2, 3, 4, 5 or 6 double bond (vinyl), preferably 1 double bond. Preferred alkenyl groups include ethenyl or vinyl (-CH=CH₂), 1-propylene or allyl (-CH₂CH=CH₂), isopropylene (-C(CH₃)=CH₂), bicyclo [2.2. 1] heptene, and the like.

[0037] The term "alkenylene" refers to a diradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2, 3, 4, 5, 6, 7, 8, 9, 10, 11,

25 12, 13, 14, 15, 16, 17, 18, 19 or 20 carbon atoms, more preferably 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms and even more preferably 2, 3, 4, 5 or 6 carbon atoms and having 1, 3, 4, 5 or 6 double bond (vinyl), preferably 1 double bond.

[0038] The term "substituted alkenyl" refers to an alkenyl group as defined above having 1, 2, 3, 4 or 5 substituents, and preferably 1, 2, or 3 substituents, selected

30 from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, aminocarbonyl,

alkoxycarbonylamino, azido, cyano, halogen, thiocarbonyl, carboxy, carboxyalkyl, -SO₃H, aryl, aryloxy, heteroaryl, aminocarbonylamino, heteroaryloxy, heterocyclyl, heterocyclyloxy, hydroxyamino, alkoxyamino, nitro, -S(O)₂NR^aR^a, -NR^aS(O)₂R^a and -S(O)_pR^b where each R^a is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl; heterocyclyloxywhere R^b is alkyl, aryl, heteroaryl or heterocyclyl and p is 0, 1 or 2. Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1, 2, or 3 substituents selected from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF₃, amino, substituted amino, cyano, and -S(O)_pR^c, where R^c is alkyl, aryl, or heteroaryl and p is 0, 1 or 2.

[0039] The term "alkynyl" refers to a monoradical of an unsaturated hydrocarbon, preferably having from 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 carbon atoms, more preferably 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms and even more preferably 2, 3, 4, 5 or 6 carbon atoms and having 1, 2, 3, 4, 5 or 6 sites of acetylene (triple bond) unsaturation, preferably 1 triple bond. Preferred alkynyl groups include ethynyl, ($\text{-C}\equiv\text{CH}$), propargyl (or prop-1-yn-3-yl, $\text{-CH}_2\text{C}\equiv\text{CH}$), homopropargyl (or but-1-yn-4-yl, $\text{-CH}_2\text{CH}_2\text{C}\equiv\text{CH}$) and the like.

[0040] The term "alkynylene" refers to a diradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 carbon atoms, more preferably 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms and even more preferably 2, 3, 4, 5 or 6 carbon atoms and having 1, 3, 4, 5 or 6 sites of acetylene (triple bond) unsaturation, preferably 1 triple bond.

25 **[0041]** The term "substituted alkynyl" refers to an alkynyl group as defined above
having 1, 2, 3, 4 or 5 substituents, and preferably 1, 2, or 3 substituents, selected
from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl,
cycloalkenyl, acyl, acylamino, acyloxy, amino, aminocarbonyl,
alkoxycarbonylamino, azido, cyano, halogen, hydroxy, keto, thiocarbonyl, carboxy,
30 carboxyalkyl, -SO₃H, aryl, aryloxy, heteroaryl, aminocarbonylamino, heteroaryloxy,
heterocyclyl, heterocyclyloxy, hydroxyamino, alkoxyamino, nitro, -S(O)₂NR^aR^a,

NR^aS(O)₂R^a and -S(O)_pR^b, where each R^a is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl heteroarylalkyl, heterocyclyl and heterocyclylalkyl; heterocycliloxy where R^b is alkyl, aryl, heteroaryl or heterocyclyl and p is 0, 1 or 2. Unless otherwise constrained
5 by the definition, all substituents may optionally be further substituted by 1, 2, or 3 substituents selected from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF₃, amino, substituted amino, cyano, and -S(O)_pR^c where R^c is alkyl, aryl, or heteroaryl and p is 0, 1 or 2.

[0042] The term "cycloalkyl" refers to carbocyclic groups of from 3 to 20 carbon
10 atoms having a single cyclic ring or multiple condensed rings which may be partially unsaturated. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cyclooctyl, and the like, or multiple ring structures such as adamantanyl, bicyclo[2.2.1]heptane, 1,3,3-trimethylbicyclo[2.2.1]hept-2-yl, 2,3,3-
15 trimethylbicyclo[2.2.1]hept-2-yl, or carbocyclic groups to which is fused an aryl group, for example indane, and the like.

[0043] The term "substituted cycloalkyl" refers to cycloalkyl groups having 1, 2, 3, 4 or 5 substituents, and preferably 1, 2, or 3 substituents, selected from the group consisting of alkyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, aminocarbonyl, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo,
20 thiocarbonyl, aryl, aryloxy, heteroaryl, aminosulfonyl, aminocarbonylamino, heteroaryloxy, heterocyclyl, heterocycliloxy, hydroxyamino, alkoxyamino, nitro, -C(O)R and -S(O)_pR^b, where R is hydrogen, hydroxyl, alkoxy, alkyl and cycloalkyl, heterocycliloxy where R^b is alkyl, aryl, heteroaryl or heterocyclyl and p is 0, 1 or 2.
25 Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1, 2, or 3 substituents selected from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF₃, amino, substituted amino, cyano, and -S(O)_pR^c, where R^c is alkyl, aryl, or heteroaryl and p is 0, 1 or 2.

[0044] "Halo" or "Halogen", alone or in combination with any other term means
30 halogens such as chloro (Cl), fluoro (F), bromo (Br) and iodo (I).

[0045] "Haloalkyl" refers to a straight chain or branched chain haloalkyl group with 1 to 6 carbon atoms. The alkyl group may be partly or totally halogenated. Representative examples of haloalkyl groups include but are not limited to fluoromethyl, chloromethyl, bromomethyl, difluoromethyl, dichloromethyl, 5 dibromomethyl, trifluoromethyl, trichloromethyl, 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, 3-fluoropropyl, 3-chloropropyl, 3-bromopropyl and the like.

[0046] The term "alkoxy" refers to the group R^{'''}-O-, where R^{'''} is optionally substituted alkyl or optionally substituted cycloalkyl, or optionally substituted 10 alkenyl or optionally substituted alkynyl; or optionally substituted cycloalkenyl, where alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl are as defined herein. Representative examples of alkoxy groups include but are not limited to methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, 1,2-dimethylbutoxy, trifluoromethoxy, and the like.

15 [0047] The term "aminocarbonyl" refers to the group -C(O)NR[']R['] where each R['] is independently hydrogen, alkyl, aryl, heteroaryl, heterocyclyl or both R['] groups are joined to form a heterocyclic group (e. g. morpholino). Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents selected from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, 20 alkoxy, halogen, CF₃, amino, substituted amino, cyano, and -S(O)_pR^c, where R^c is alkyl, aryl, or heteroaryl and p is 0, 1 or 2.

[0048] The term "acylamino" refers to the group -NR^{''}C(O)R^{''} where each R^{''} is independently hydrogen, alkyl, aryl, heteroaryl, or heterocyclyl. Unless otherwise 25 constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents selected from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF₃, amino, substituted amino, cyano, and -S(O)_pR^c, where R^c is alkyl, aryl, or heteroaryl and p is 0, 1 or 2.

[0049] The term "acyloxy" refers to the groups -OC(O)-alkyl, -OC(O)-cycloalkyl, -OC(O)-aryl, -OC(O)-heteroaryl, and -OC(O)-heterocyclyl. Unless 30 constrained by the definition, all substituents may be optionally further substituted by alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF₃,

amino, substituted amino, cyano, or $-S(O)_pR^c$, where R^c is alkyl, aryl, or heteroaryl and p is 0, 1 or 2.

[0050] The term “alkoxyalkyl” refers to alkyl groups as defined above wherein at least one of the hydrogen atoms of the alkyl group is replaced by an alkoxy group as defined above. Representative examples of alkoxyalkyl groups include but are not limited to methoxymethyl, methoxyethyl, ethoxymethyl and the like.

[0051] The term “aryloxyalkyl” refers to the group $-alkyl-O-aryl$. Representative examples of aryloxyalkyl include but are not limited to phenoxymethyl, naphthyloxymethyl, phenoxyethyl, naphthyloxyethyl and the like.

[0052] The term “di alkylamino” refers to an amino group, to which two same or different straight chain or branched chain alkyl groups with 1 to 6 carbon atoms are bound. Representative examples of di alkylamino include but are not limited to dimethylamino, diethylamino, methylethylamino, dipropylamino, dibutylamino and the like.

[0053] The term “cycloalkylalkyl” refers to an alkyl radical as defined above which is substituted by a cycloalkyl radical as defined above. Representative examples of cycloalkylalkyl include but are not limited to cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 1-cyclopentylethyl, 1-cyclohexylethyl, 2-cyclopentylethyl, 2-cyclohexylethyl, cyclobutylpropyl, cyclopentylpropyl, cyclohexylbutyl and the like.

[0054] The term “aminoalkyl” refers to an amino group that is attached to (C_{1-6}) alkylene as defined herein. Representative examples of aminoalkyl include but are not limited to aminomethyl, aminoethyl, 1-aminopropyl, 2-aminopropyl, and the like. The amino moiety of aminoalkyl may be substituted once or twice with alkyl to provide alkylaminoalkyl and dialkylaminoalkyl respectively. Representative examples of alkylaminoalkyl include but are not limited to methylaminomethyl, methylaminoethyl, methylaminopropyl, ethylaminoethyl and the like. Representative examples of dialkylaminoalkyl include but are not limited to dimethylaminomethyl, dimethylaminoethyl, dimethylaminopropyl, N-methyl-N-ethylaminoethyl and the like.

[0055] The term "aryl" refers to an aromatic carbocyclic group of 6 to 20 carbon atoms having a single ring (e.g. phenyl) or multiple rings (e.g. biphenyl), or multiple condensed (fused) rings (e.g. naphthyl or anthranyl). Preferred aryls include phenyl, naphthyl and the like.

5 [0056] The term "arylene" refers to a diradical of an aryl group as defined above. This term is exemplified by groups such as 1,4-phenylene, 1,3-phenylene, 1,2-phenylene, 1,4'-biphenylene, and the like.

[0057] Unless otherwise constrained the aryl or arylene groups may optionally be substituted with 1, 2, 3 4 or 5 substituents, preferably 1, 2 or 3 substituents, selected
10 from the group consisting of alkyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, aminocarbonyl, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, carboxy, carboxyalkyl, -SO₃H, aryl, aryloxy, heteroaryl, aminosulfonyl, aminocarbonylamino, heteroaryloxy, heterocyclyl, heterocyclyloxy, hydroxyamino, alkoxyamino, nitro, -S(O)₂NR^aR^a, -NR^aS(O)₂R^a and -S(O)_pR^b where
15 each R^a is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl; where R^b is hydrogen, alkyl, aryl, heterocyclyl or heteroaryl and p is 0, 1 or 2. Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1, 2 or 3 substituents selected from alkyl,
20 carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF₃, amino, substituted amino, cyano, and -S(O)_pR^c where R^c is hydrogen, alkyl, aryl, or heteroaryl and p is 0, 1 or 2.

[0058] The term "arylalkyl" refers to an aryl group covalently linked to an alkylene group, where aryl and alkylene are defined herein.

25 [0059] The term "optionally substituted arylalkyl" refers to an optionally substituted aryl group covalently linked to an optionally substituted alkylene group. Such arylalkyl groups are exemplified by benzyl, phenethyl, naphthylmethyl, and the like.

[0060] The term "aryloxy" refers to the group -O-aryl, wherein the aryl group is as defined above and includes optionally substituted aryl groups as also defined above.

30 [0061] The term "arylthio" refers to the group -S-aryl, where aryl group is as defined herein including optionally substituted aryl groups as also defined above.

[0062] The term "substituted amino" refers to the group $-NR'R'$ where each R' is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, carboxyalkyl, alkoxy carbonyl, aryl, heteroaryl and heterocyclyl. Unless otherwise constrained by the definition, all substituents may optionally be further substituted
5 by 1, 2 or 3 substituents selected from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3 , amino, substituted amino, cyano, and $-S(O)_pR^c$, where R^c is alkyl, aryl, or heteroaryl and p is 0, 1 or 2.

[0063] The term "carboxyalkyl" refers to the group $-alkylene-C(O)OH$.

[0064] The term "alkylcarboxyalkyl" refers to the group $-alkylene-C(O)OR^d$ where
10 R^d is alkyl, cycloalkyl, where alkyl, cycloalkyl are as defined herein, and may be optionally further substituted by alkyl, halogen, CF_3 , amino, substituted amino, cyano, or $-S(O)_pR^c$, in which R^c is alkyl, aryl, or heteroaryl and p is 0, 1 or 2.

[0065] The term "heteroaryl" refers to an aromatic cyclic group having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 carbon atoms and 1, 2, 3 or 4 heteroatoms selected
15 from oxygen, nitrogen and sulfur within at least one ring. Such heteroaryl groups can have a single ring (e.g. pyridyl or furyl) or multiple condensed rings (e.g. indoliziny, benzothiazolyl, or benzothienyl). Examples of heteroaryls include, but are not limited to, [1,2,4] oxadiazole, [1,3,4] oxadiazole, [1,2,4] thiadiazole, [1,3,4] thiadiazole, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine,
20 indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, furan, thiophene, oxazole, thiazole, triazole, triazine and the like.

25 [0066] The term "heteroarylene" refers to a diradical of a heteroaryl group as defined above.

[0067] Unless otherwise constrained the heteroaryl or heterarylene groups can be optionally substituted with 1, 2, 3, 4 or 5 substituents, preferably 1, 2 or 3 substituents selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl,
30 cycloalkenyl, acyl, acylamino, acyloxy, amino, aminocarbonyl, alkoxy carbonylamino, azido, cyano, halogen, hydroxy, thiocarbonyl, carboxy,

carboxyalkyl, $-\text{SO}_3\text{H}$, aryl, aryloxy, heteroaryl, aminocarbonylamino, heteroaryloxy, heterocyclyl, heterocyclyloxy, hydroxyamino, alkoxyamino, nitro, $-\text{S}(\text{O})_2\text{NR}^a$, $-\text{NR}^a\text{S}(\text{O})_2\text{R}^a$ and $-\text{S}(\text{O})_p\text{R}^b$, where each R^a is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl
5 heteroarylalkyl, heterocyclyl and heterocyclylalkyl; where R^b is hydrogen, alkyl, aryl, heterocyclyl or heteroaryl, and p is 0, 1 or 2. Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents selected from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3 , amino, substituted amino, cyano, and $-\text{S}(\text{O})_n\text{R}^c$, where R^c is
10 alkyl, aryl, or heteroaryl and n is 0, 1 or 2.

[0068] The term "heteroarylalkyl" refers to a heteroaryl group covalently linked to an alkylene group, where heteroaryl and alkylene are defined herein.

[0069] The term "optionally substituted heteroarylalkyl" refers to an optionally substituted heteroaryl group covalently linked to an optionally substituted alkylene
15 group. Such heteroarylalkyl groups are exemplified by 3-pyridylmethyl, quinolin-8-ylethyl, 4-methoxythiazol-2-ylpropyl, and the like.

[0070] The term "heterocyclyl" refers to a saturated or partially unsaturated group having a single ring or multiple condensed rings, having from 1 to 40 carbon atoms and from 1 to 10 hetero atoms, preferably 1, 2, 3 or 4 heteroatoms, selected from
20 nitrogen, sulfur, phosphorus, and/or oxygen within the ring. Heterocyclic groups can have a single ring or multiple condensed rings, and include tetrahydrofuranyl, morpholinyl, piperidinyl, piperazinyl, dihydropyridinyl, tetrahydroquinolinyl and the like. Unless otherwise constrained by the definition for the heterocyclic substituent, such heterocyclic groups can be optionally substituted with 1, 2, 3, 4 or
25 5, and preferably 1, 2 or 3 substituents, selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, aminocarbonyl, alkoxy-carbonylamino, azido, cyano, halogen, hydroxy, oxo, $-\text{C}(\text{O})\text{R}$ where R is hydrogen, hydroxyl, alkoxy, alkyl and cycloalkyl, thiocarbonyl, carboxy, carboxyalkyl, aryl, aryloxy, heteroaryl, aminosulfonyl,
30 aminocarbonylamino, heteroaryloxy, heterocyclyl, heterocyclyloxy, hydroxyamino, alkoxyamino, nitro, and $-\text{S}(\text{O})_p\text{R}^b$, where R^b is hydrogen, alkyl, aryl, heterocyclyl or

heteroaryl and p is 0, 1 or 2. Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents selected from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF₃, amino, substituted amino, cyano, and -S(O)R^c, where R^c is alkyl, aryl, or heteroaryl and n is 0, 1 or 2.

[0071] The term "heterocyclalkyl" refers to a heterocycl group covalently linked to an alkylene group, where heterocycl and alkylene are defined herein.

[0072] The term "optionally substituted heterocyclalkyl" refers to an optionally substituted heterocycl group covalently linked to an optionally substituted alkylene group.

[0073] The term "heteroaryloxy" refers to the group -O-heteroaryl.

[0074] The term "thiol" refers to the group -SH.

[0075] The term "carboxy" refers to -C(O).

[0076] The term "substituted alkylthio" refers to the group -S-substituted alkyl.

[0077] The term "heteroarylthio" refers to the group -S-heteroaryl wherein the heteroaryl group is as defined above including optionally substituted heteroaryl groups as also defined above.

[0078] The term "sulfoxide" refers to a group -S(O).

[0079] The term "substituted sulfoxide" refers to a group -S(O)R, in which R is substituted alkyl, substituted aryl, or substituted heteroaryl, as defined above.

[0080] The term "sulfone" refers to a group -S(O)₂R, where R is alkyl, aryl, or heteroaryl.

[0081] The term "substituted sulfone" refers to a group -S(O)₂R, in which R is alkyl, aryl, or heteroaryl.

[0082] The term "disorder or condition ameliorated by the inhibition of the A_{2A} receptor" will be understood by those skilled in the art to include: cancer such as prostate, rectal, renal, ovarian, endometrial, thyroid, pancreatic, particularly breast, colon, bladder, brain, glia, melanoma, pineal gland and, more particularly, lung cancer (e.g. Lewis lung carcinoma).

[0083] The compounds of the present disclosure may have the ability to crystallize in more than one form, a characteristic known as polymorphism, and all such

polymorphic forms ("polymorphs") are encompassed within the scope of the invention. Polymorphism generally can occur as a response to changes in temperature or pressure or both and can also result from variations in the crystallization process. Polymorphs can be distinguished by various physical characteristics, and typically the x-ray diffraction patterns, solubility behavior, and melting point of the compound are used to distinguish polymorphs.

[0084] The compounds described herein may contain one or more chiral centers and/or double bonds and therefore, may exist as "stereoisomers", such as double-bond isomers (i.e., "geometric isomers"), regioisomers, enantiomers or diastereomers. Accordingly, the chemical structures depicted herein encompass all possible enantiomers and stereoisomers of the illustrated or identified compounds including the stereoisomerically pure form (e.g., geometrically pure, enantiomerically pure or diastereomerically pure) and enantiomeric and stereoisomeric mixtures. Enantiomeric and stereoisomeric mixtures can be resolved into their component enantiomers or stereoisomers using separation techniques or chiral synthesis techniques well known to the person skilled in the art. The compounds may also exist in several tautomeric forms including the enol form, the keto form and mixtures thereof.

[0085] Accordingly, the chemical structures depicted herein encompass all possible tautomeric forms of the illustrated or identified compounds.

[0086] Compounds may exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, compounds may be hydrated, solvated or N-oxides. Certain compounds may exist in multiple crystalline or amorphous forms. Also contemplated within the scope of the invention are congeners, analogs, hydrolysis products, metabolites and precursor or prodrugs of the compound. In general, unless otherwise indicated, all physical forms are equivalent for the uses contemplated herein and are intended to be within the scope of the present invention.

[0087] The term "prodrug" refers to a derivative of a drug molecule as, for example, esters, carbonates, carbamates, ureas, amides or phosphates that requires a transformation within the body to release the active drug. Prodrugs are frequently, although not necessarily, pharmacologically inactive until converted to the parent

drug. Prodrugs may be obtained by bonding a promoiety (defined herein) typically via a functional group, to a drug.

[0088] The term "therapeutically effective dose" means an amount of a compound or composition which is sufficient enough to significantly and positively modify the symptoms and/or conditions to be treated (e.g., provide a positive clinical response). The effective amount of an active ingredient for use in a pharmaceutical composition will vary with the particular condition being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the particular active ingredient(s) being employed, the particular pharmaceutically-acceptable excipient(s)/carrier(s) utilized, the route of administration, and like factors within the knowledge and expertise of the attending physician.

[0089] The term "promoiety" refers to a group bonded to a drug, typically to a functional group of the drug, via bond(s) that are cleavable under specified conditions of use. The bond(s) between the drug and promoiety may be cleaved by enzymatic or non-enzymatic means. Under the conditions of use, for example following administration to a patient, the bond(s) between the drug and promoiety may be cleaved to release the parent drug. The cleavage of the promoiety may proceed spontaneously, such as via a hydrolysis reaction, or it may be catalyzed or induced by another agent, such as by an enzyme, by light, by acid, or by a change of or exposure to a physical or environmental parameter, such as a change of temperature, pH, etc. The agent may be endogenous to the conditions of use, such as an enzyme present in the systemic circulation to which the prodrug is administered or the acidic conditions of the stomach or the agent may be supplied exogenously.

[0090] The phrase "pharmaceutically acceptable excipient" refers to compounds or compositions that are physiologically tolerable and do not typically produce allergic or similar untoward reactions, including but not limited to gastric upset or dizziness when administered to mammal.

[0091] The term "pharmaceutically acceptable salt" embraces salts with a pharmaceutically acceptable acid or base. Pharmaceutically acceptable acids include both inorganic acids, for example hydrochloric, sulphuric, phosphoric, diphosphoric, hydrobromic, hydroiodic and nitric acid and organic acids, for example citric,

fumaric, maleic, malic, mandelic, ascorbic, oxalic, succinic, tartaric, benzoic, acetic, methanesulphonic, ethanesulphonic, benzenesulphonic or p-toluenesulphonic acid. Pharmaceutically acceptable bases include alkali metal (e.g. sodium or potassium) and alkali earth metal (e.g. calcium or magnesium) hydroxides and organic bases,
5 for example alkyl amines, arylalkyl amines and heterocyclic amines.

[0092] Other preferred salts according to the invention are quaternary ammonium compounds wherein an equivalent of an anion (X-) is associated with the positive charge of the N atom. X- may be an anion of various mineral acids such as, for example, chloride, bromide, iodide, sulphate, nitrate, phosphate, or an anion of an
10 organic acid such as, for example, acetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, trifluoroacetate, methanesulphonate and p-toluenesulphonate. X- is preferably an anion selected from chloride, bromide, iodide, sulphate, nitrate, acetate, maleate, oxalate, succinate or trifluoroacetate. More preferably X- is chloride, bromide, trifluoroacetate or methanesulphonate.

[0093] The terms "solvent", "inert organic solvent" or "inert solvent" mean a solvent inert under the conditions of the reaction being described in conjunction therewith [including, for example, benzene, toluene, acetonitrile, tetrahydrofuran ("THF"), dimethylformamide ("DMF"), chloroform, methylene chloride (or
15 dichloromethane), diethyl ether, methanol, pyridine and the like]. Unless specified to the contrary, the solvents used in the reactions of the present disclosure are inert
20 organic solvents. The term "q.s." means adding a quantity sufficient to achieve a stated function, e.g., to bring a solution to the desired volume (i.e., 100%).

[0094] Furthermore, the compound of Formula I can be its derivatives, analogs, stereoisomer's, diastereomers, geometrical isomers, polymorphs, solvates, co-
25 crystals, intermediates, hydrates, metabolites, prodrugs or pharmaceutically acceptable salts and compositions.

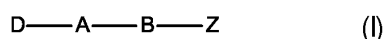
[0095] It is understood that included in the family of compounds of Formula I are isomeric forms including diastereoisomers, enantiomers, tautomers, and geometrical isomers in "E" or "Z" configurational isomer or a mixture of E and Z isomers. It is
30 also understood that some isomeric forms such as diastereomers, enantiomers and

geometrical isomers can be separated by physical and/or chemical methods by those skilled in the art.

[0096] Compounds disclosed herein may exist as single stereoisomers, racemates and or mixtures of enantiomers and/or diastereomers. All such single stereoisomers, racemates and mixtures thereof are intended to be within the scope of the subject matter described.

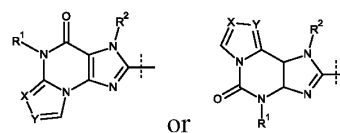
[0097] Compounds disclosed herein include isotopes of hydrogen, carbon, oxygen, fluorine, chlorine, iodine and sulfur which can be incorporated into the compounds, such as, but not limited to, ^2H (D), ^3H (T), ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}F , ^{35}S , ^{36}Cl , and ^{125}I . Compounds of this disclosure wherein atoms were isotopically labeled for example radioisotopes such as ^3H , ^{13}C , ^{14}C , and the like can be used in metabolic studies, kinetic studies, and imaging techniques such as positron emission tomography used in understanding the tissue distribution of the drugs. Compounds of the disclosure where hydrogen is replaced with deuterium may improve the metabolic stability, and pharmacokinetics properties of the drug such as in vivo half-life.

[0098] In an embodiment of the present disclosure, there is provided a compound of Formula I, or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, prodrugs, racemic mixtures, optically active forms and pharmaceutically active derivatives thereof,



Formula I

wherein



D represents a tricyclic ring system selected from

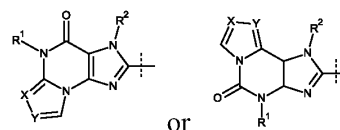
wherein R^1 is selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl;

R^2 is selected from hydrogen, alkyl, alkenyl, alkynyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl;

- wherein alkyl, alkenyl, alkynyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl are unsubstituted or substituted independently with alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, monoalkylamino, dialkylamino, arylamino, cycloalkylamino, heteroarylamino, heterocyclamino, aminocarbonyl, alkoxy carbonylamino, azido, cyano, halogen, hydroxy, hydroxyalkyl, keto, thiocarbonyl, carboxy, alkylcarboxy, carboxyalkyl, carboxyalkyloxy, alkylcarboxyalkyloxy, -SO₃H, aryl, aryloxy, cycloalkyloxy, heteroaryl, aminocarbonylamino, heteroaryloxy, heterocyclyl, heterocyclioxy, hydroxyamino, alkoxyamino, nitro, S(O)₂NR^cR^c, -NR^cS(O)₂R^c or -S(O)_pR^d;
- wherein each substituent is unsubstituted or substituted with 1, 2, or 3 substituents independently selected from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, haloalkyl, haloalkoxy, amino, substituted amino, cyano or -S(O)_pR^d;
- X and Y are independently selected from CR' or N, wherein R' is selected from hydrogen, halogen, alkyl and haloalkyl;
- A is selected from an optionally substituted arylene or an optionally substituted heteroarylene;
- B is selected from a bond, (C₁-C₆)alkylene, (C₂-C₆)alkenylene or (C₂-C₆)alkynylene group, wherein 1 to 4 methylene groups are optionally replaced by groups independently selected from O, -S(O)_p-, -N(R^b)-, or -C(O)-;
- wherein alkylene, alkenylene, and alkynylene are unsubstituted or substituted independently with alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, monoalkylamino, dialkylamino, arylamino, cycloalkylamino, heteroarylamino, heterocyclamino, aminocarbonyl, alkoxy carbonylamino, azido, cyano, halogen, hydroxy, hydroxyalkyl, keto, thiocarbonyl, carboxy, alkylcarboxy, carboxyalkyl, carboxyalkyloxy, alkylcarboxyalkyloxy -SO₃H, aryl, aryloxy, cycloalkyloxy, heteroaryl, aminocarbonylamino, heteroaryloxy, heterocyclyl, heterocyclioxy, hydroxyamino, alkoxyamino, nitro, S(O)₂NR^cR^c, -NR^cS(O)₂R^c or -S(O)_pR^d;
- Z is selected from hydrogen, heterocyclyl, cycloalkyl, aryl or heteroaryl;

- wherein heterocyclyl, cycloalkyl, aryl and heteroaryl are unsubstituted or substituted independently with alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, monoalkylamino, dialkylamino, arylamino, cycloalkylamino, heteroarylamino, heterocyclylamino, aminocarbonyl, alkoxy carbonylamino, azido, cyano, halogen, hydroxy, hydroxyalkyl, keto, thiocarbonyl, carboxy, alkylcarboxy, carboxyalkyl, carboxyalkyloxy, alkylcarboxyalkyloxy -SO₃H, aryl, arylalkyl, aryloxy, cycloalkyloxy, heteroaryl, heteroarylalkyl, aminocarbonylamino, heteroaryloxy, heterocyclyl, heterocyclylalkyl, heterocyclyoxy, hydroxyamino, alkoxyamino, nitro, -S(O)₂NR^bR^b, -NR^bS(O)₂R^b or -S(O)_pR^d;
- wherein each substituent is unsubstituted or substituted with 1, 2, or 3 substituents independently selected from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, alkoxyalkoxy, alkoxyalkyl, halogen, haloalkyl, haloalkoxy, amino, substituted amino, cyano or -S(O)_pR^d;
- R^a is selected from hydrogen, or alkyl;
- R^b is selected from hydrogen, alkyl, acyl, carboxyalkyl, carbonylamino, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, or heterocyclylalkyl;
- R^c is selected from hydrogen, alkyl, aryl, heteroaryl, or heterocyclyl;
- R^d is selected from alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl; and
- p is 0, 1, or 2.

- [0099] In an embodiment of the present disclosure there is provided a compound of Formula I, or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, prodrugs, racemic mixtures, optically active forms and pharmaceutically active derivatives thereof, wherein



D represents a tricyclic ring system selected from

wherein R¹ is selected from alkyl, cycloalkyl, aryl, arylalkyl, heterocyclyl, heteroaryl, or heteroarylalkyl;

R^2 is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl are unsubstituted or substituted independently with alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, acyl, acylamino, amino, monoalkylamino, dialkylamino, arylamino, cycloalkylamino, heteroarylamino, heterocyclylamino, aminocarbonyl, azido, cyano, halogen, hydroxy, hydroxyalkyl, keto, thiocarbonyl, carboxy, alkylcarboxy, carboxyalkyl, , -SO₃H, aryl, cycloalkyloxy, heteroaryl, aminocarbonylamino, heterocyclyl, heterocycliloxy, hydroxyamino, nitro, S(O)₂NR^cR^c, -NR^cS(O)₂R^c or -S(O)_pR^d;

wherein each substituent is unsubstituted or substituted with 1, 2, or 3 substituents independently selected from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, haloalkyl, haloalkoxy, amino, substituted amino, cyano or -S(O)_pR^d;

X and Y are independently selected from CR' or N, wherein R' is selected from hydrogen, halogen, or alkyl;

A is selected from an optionally substituted arylene or an optionally substituted heteroarylene;

B is selected from a bond, (C₁-C₆)alkylene, or (C₂-C₆)alkynylene group, wherein 1 to 3 methylene groups are optionally replaced by groups independently selected from O, -S(O)_p-, or -C(O)-;

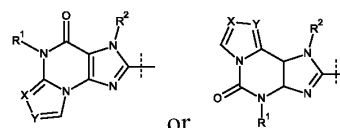
wherein alkylene, and alkynylene are unsubstituted or substituted independently with alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acyloxy, azido, cyano, halogen, hydroxy, hydroxyalkyl, keto, thiocarbonyl, carboxy, alkylcarboxy, carboxyalkyl, carboxyalkyloxy, alkylcarboxyalkyloxy -SO₃H, aryl, aryloxy, cycloalkyloxy, heteroaryl, heteroaryloxy, heterocyclyl, heterocycliloxy, hydroxyamino, nitro, S(O)₂NR^cR^c, or -S(O)_pR^d;

Z is selected from hydrogen, heterocyclyl, cycloalkyl, aryl or heteroaryl;

wherein heterocyclyl, cycloalkyl, aryl and heteroaryl are unsubstituted or substituted independently with alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, monoalkylamino, dialkylamino, arylamino, cycloalkylamino, heteroarylamino, heterocyclylamino, aminocarbonyl,

- alkoxycarbonylamino, cyano, halogen, hydroxy, hydroxyalkyl, keto, thiocarbonyl, carboxy, alkylcarboxy, carboxyalkyl, carboxyalkyloxy, alkylcarboxyalkyloxy, aryl, arylalkyl, aryloxy, cycloalkyloxy, heteroaryl, heteroarylalkyl, aminocarbonylamino, heteroaryloxy, heterocyclyl, heterocyclylalkyl, heterocycliloxy, hydroxyamino,
- 5 alkoxyamino, $-S(O)_2NR^bR^b$, $-NR^bS(O)_2R^b$ or $-S(O)_pR^d$;
- wherein each substituent is unsubstituted or substituted with 1, 2, or 3 substituents independently selected from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, alkoxyalkoxy, alkoxyalkyl, halogen, haloalkyl, haloalkoxy, amino, substituted amino;
- 10 R^a is selected from hydrogen, or alkyl;
- R^b is selected from hydrogen, alkyl, acyl, carboxyalkyl, carbonylamino, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, or heterocyclylalkyl;
- R^c is selected from hydrogen, alkyl, aryl, heteroaryl, or heterocyclyl;
- 15 R^d is selected from alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl; and
- p is 0, 1, or 2.

- [00100]** In an embodiment of the present disclosure there is provided a compound of Formula I, or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, prodrugs, racemic mixtures,
- 20 optically active forms and pharmaceutically active derivatives thereof, wherein



- D represents a tricyclic ring system selected from
- wherein R^1 is selected from alkyl, cycloalkyl, aryl, or arylalkyl,
- R^2 is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, or aryl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, are unsubstituted or substituted
- 25 independently with alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, acyl, acylamino, amino, monoalkylamino, dialkylamino, arylamino, cycloalkylamino, heteroarylamino, heterocyclylamino, aminocarbonyl, azido, cyano, halogen, hydroxy, hydroxyalkyl, keto, thiocarbonyl, carboxy, alkylcarboxy, carboxyalkyl, , -

- SO₃H, aryl, cycloalkyloxy, heteroaryl, aminocarbonylamino, heterocyclyl, heterocyclyloxy, hydroxyamino, nitro, S(O)₂NR^cR^c, -NR^cS(O)₂R^c or -S(O)_pR^d;
 wherein each substituent is unsubstituted or substituted with 1, 2, or 3 substituents independently selected from alkyl, carboxy, carboxyalkyl, aminocarbonyl,
 5 hydroxyd, alkoxy, halogen, haloalkyl, haloalkoxy, amino, substituted amino, cyano or -S(O)_pR^d;
 X and Y are independently selected from CR' or N, wherein R' is selected from hydrogen, halogen, or alkyl;
 A is selected from an optionally substituted arylene or an optionally substituted
 10 heteroarylene;
 B is selected from a bond, (C₁-C₆)alkylene, or (C₂-C₆)alkynylene group, wherein 1 to 3 methylene groups are optionally replaced by groups independently selected from O, -S(O)_p-, or -C(O)-;
 wherein alkylene, and alkynylene are unsubstituted or substituted independently
 15 with alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acyloxy, azido, cyano, halogen, hydroxy, hydroxyalkyl, keto, thiocarbonyl, carboxy, alkylcarboxy, carboxyalkyl, carboxyalkyloxy, alkylcarboxyalkyloxy -SO₃H, aryl, aryloxy, cycloalkyloxy, heteroaryl, heteroaryloxy, heterocyclyl, heterocyclyloxy, hydroxyamino, nitro, S(O)₂NR^cR^c, or -S(O)_pR^d;
 20 Z is selected from hydrogen, heterocyclyl, cycloalkyl, aryl or heteroaryl;
 wherein heterocyclyl, cycloalkyl, aryl and heteroaryl are unsubstituted or substituted independently with alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, monoalkylamino, dialkylamino, arylamino, cycloalkylamino, heteroarylamino, heterocyclylamino, aminocarbonyl,
 25 alkoxycarbonylamino, cyano, halogen, hydroxy, hydroxyalkyl, keto, thiocarbonyl, carboxy, alkylcarboxy, carboxyalkyl, carboxyalkyloxy, alkylcarboxyalkyloxy, aryl, arylalkyl, aryloxy, cycloalkyloxy, heteroaryl, heteroarylalkyl, aminocarbonylamino, heteroaryloxy, heterocyclyl, heterocyclylalkyl, heterocyclyloxy, hydroxyamino, alkoxyamino, -S(O)₂NR^bR^b, -NR^bS(O)₂R^b or -S(O)_pR^d;
 30 wherein each substituent is unsubstituted or substituted with 1, 2, or 3 substituents independently selected from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy,

alkoxy, alkoxyalkoxy, alkoxyalkyl, halogen, haloalkyl, haloalkoxy, amino, substituted amino;

R^a is selected from hydrogen, or alkyl;

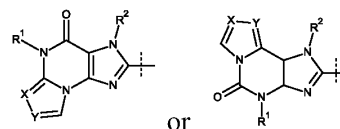
R^b is selected from hydrogen, alkyl, aryl, arylalkyl, heteroaryl, or heterocyclylalkyl;

5 R^c is selected from hydrogen, alkyl, aryl, heteroaryl, or heterocyclyl;

R^d is selected from alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl; and

p is 1, or 2.

[00101] In an embodiment of the present disclosure there is provided a compound of Formula I, or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, prodrugs, racemic mixtures,
10 optically active forms and pharmaceutically active derivatives thereof, wherein



D represents a tricyclic ring system selected from

wherein R^1 is selected from alkyl;

R^2 is selected from hydrogen, or alkyl, wherein alkyl, is unsubstituted or substituted
15 independently with alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, acyl, acylamino, amino, monoalkylamino, dialkylamino, cycloalkylamino, heteroaryl, aminocarbonylamino, heterocyclyl, heterocyclyloxy, hydroxyamino, nitro, $S(O)_2NR^cR^c$, $-NR^cS(O)_2R^c$ or $-S(O)_pR^d$;

wherein each substituent is unsubstituted or substituted with 1, 2, or 3 substituents

20 independently selected from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxyd, alkoxy, halogen, haloalkyl, haloalkoxy, amino, substituted amino, cyano or $-S(O)_pR^d$;

X and Y are independently selected from CR' or N, wherein R' is selected from hydrogen, halogen, or alkyl;

25 A is selected from an optionally substituted arylene or an optionally substituted heteroarylene;

B is selected from a bond, (C_1-C_6) alkylene, or (C_2-C_6) alkynylene group, wherein 1 to 3 methylene groups are optionally replaced by groups independently selected from O, $-S(O)_p-$, or $-C(O)-$;

- wherein alkylene, and alkynylene are unsubstituted or substituted independently with alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acyloxy, azido, cyano, halogen, hydroxy, hydroxyalkyl, keto, thiocarbonyl, carboxy, alkylcarboxy, carboxyalkyl, carboxyalkyloxy, alkylcarboxyalkyloxy -SO₃H, aryl, aryloxy, cycloalkyloxy, heteroaryl, heteroaryloxy, heterocyclyl, heterocyclyloxy, hydroxyamino, nitro, S(O)₂NR^cR^c, or -S(O)_pR^d;
- 5 Z is selected from hydrogen, heterocyclyl, aryl or heteroaryl;
- wherein heterocyclyl, aryl and heteroaryl are unsubstituted or substituted independently with alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, monoalkylamino, dialkylamino, arylamino, cycloalkylamino, heteroarylamino, heterocyclylamino, aminocarbonyl, alkoxy carbonylamino, halogen, hydroxy, hydroxyalkyl, keto, thiocarbonyl, carboxy, aryl, arylalkyl, aryloxy, cycloalkyloxy, heteroaryl, heteroarylalkyl, heteroaryloxy, heterocyclyl, heterocyclylalkyl, heterocyclyloxy, -S(O)₂NR^bR^b, -NR^bS(O)₂R^b or -
- 15 S(O)_pR^d;
- wherein each substituent is unsubstituted or substituted with 1, 2, or 3 substituents independently selected from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, alkoxyalkoxy, alkoxyalkyl, halogen, haloalkyl, haloalkoxy, amino, substituted amino;
- 20 R^a is selected from hydrogen, or alkyl;
- R^b is selected from hydrogen, alkyl, aryl, arylalkyl, heteroaryl, or heterocyclylalkyl;
- R^c is selected from hydrogen, alkyl, aryl, heteroaryl, or heterocyclyl;
- R^d is selected from alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl; and
- p is 0, 1, or 2.
- 25 **[00102]** In an embodiment of the present disclosure there is provided a compound of Formula I, or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, prodrugs, racemic mixtures, optically active forms and pharmaceutically active derivatives thereof, wherein the compound of Formula I is selected from the group consisting of:
- 30 5-propyl-2-[1-[[3-(trifluoromethyl)phenyl]methyl]pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (**A1**),

- 2-(1-benzylpyrazol-4-yl)-5-propyl-3H-imidazo[2,1-b]purin-4-one (**A2**),
5-methyl-2-[1-[[3-(trifluoromethyl)phenyl]methyl]pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (**A3**),
5-propyl-2-[1-[2-[3-(trifluoromethyl)phenyl]ethyl]pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (**A4**),
5 2-[1-[2-(3-fluorophenyl)ethyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**A5**),
2-(1-methylpyrazol-4-yl)-5-propyl-3H-imidazo [2, 1-b] purin-4-one (**A6**),
2-[1-(1,1-dimethylpropyl)pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one
10 (**A7**),
N-isopropyl-3-[3-[4-(4-oxo-5-propyl-3H-imidazo[2,1-b]purin-2-yl)pyrazol-1-yl]prop-1-ynyl]benzamide (**B1**),
Ethyl 3-[3-[4-(4-oxo-5-propyl-3H-imidazo[2,1-b]purin-2-yl)pyrazol-1-yl]prop-1-ynyl]benzoate (**B2**),
15 5-propyl-2-[1-[3-[3-(trifluoromethoxy)phenyl]prop-2-ynyl]pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (**B3**),
Ethyl 4-methyl-3-[3-[4-(4-oxo-5-propyl-3H-imidazo[2,1-b]purin-2-yl)pyrazol-1-yl]prop-1-ynyl]benzoate (**B6**),
3-[[4-(4-oxo-5-propyl-3H-imidazo[2,1-b]purin-2-yl)pyrazol-1-yl]methyl]benzonitrile (**B7**),
20 2-(1-isopropylpyrazol-4-yl)-5-propyl-3H-imidazo[2,1-b]purin-4-one (**B8**),
2-(1-butylpyrazol-4-yl)-5-propyl-3H-imidazo[2,1-b]purin-4-one (**B9**),
2-(1-ethylpyrazol-4-yl)-5-propyl-3H-imidazo[2,1-b]purin-4-one (**B10**),
2-[1-(2-methoxyethyl)pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**B11**),
25 2-[1-(2-dimethylaminoethyl)pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**B12**),
5-propyl-2-(1-propylpyrazol-4-yl)-3H-imidazo[2,1-b]purin-4-one (**B13**),
N,N-dimethyl-2-[4-(4-oxo-5-propyl-3H-imidazo[2,1-b]purin-2-yl)pyrazol-1-yl]acetamide (**B14**),
30 2-[1-(2-morpholinoethyl)pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**B15**),

- 2-[1-(cyclobutylmethyl)pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one
(B16),
2-(1-isobutylpyrazol-4-yl)-5-propyl-3H-imidazo[2,1-b]purin-4-one (B17),
2-[1-(cyclopropylmethyl)pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one
5 (B18),
2-[1-(2,2-dimethylpropyl)pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one
(B19),
5-propyl-2-(1-sec-butylpyrazol-4-yl)-3H-imidazo[2,1-b]purin-4-one (B20),
5-propyl-2-[1-(tetrahydrofuran-2-ylmethyl)pyrazol-4-yl]-3H-imidazo[2,1-b]purin-
10 4-one (B21),
2-[1-[[5-oxo-1-[2-(trifluoromethyl)-4-pyridyl]pyrrolidin-3-yl]methyl]pyrazol-4-yl]-
5-propyl-3H-imidazo[2,1-b]purin-4-one (C1),
2-[1-[[5-oxo-1-[5-(trifluoromethyl)-3-pyridyl]pyrrolidin-3-yl]methyl]pyrazol-4-yl]-
5-propyl-3H-imidazo[2,1-b]purin-4-one (C2),
15 2-[1-[[5-oxo-1-[3-(trifluoromethyl)phenyl]pyrrolidin-3-yl]methyl]pyrazol-4-yl]-5-
propyl-3H-imidazo[2,1-b]purin-4-one (C3),
2-[1-[2-(1-piperidyl)ethyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one
(D1),
2-[1-[[3-(hydroxymethyl)phenyl]methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-
20 b]purin-4-one (E1),
2-[1-[[3-(1-hydroxy-1-methyl-ethyl)phenyl]methyl]pyrazol-4-yl]-5-propyl-3H-
imidazo[2,1-b]purin-4-one (F1),
3-[[4-(4-oxo-5-propyl-3H-imidazo[2,1-b]purin-2-yl)pyrazol-1-yl]methyl]benzoic
acid (G1),
25 2-[4-(4-oxo-5-propyl-3H-imidazo[2,1-b]purin-2-yl)pyrazol-1-yl]acetic acid (H1),
2-[1-(2-hydroxy-2-methyl-propyl)pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-
4-one (I1),
2-[1-(2,3-dihydroxypropyl)pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one
(J1),
30 2-(3,4-dimethoxyphenyl)-5-propyl-3H-imidazo[2,1-b]purin-4-one (K1),
5-propyl-2-[3-(trifluoromethyl)phenyl]-3H-imidazo[2,1-b]purin-4-one (K2),

- 2-[1-[(3-fluorophenyl)methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**K3**),
- 2-[1-[(3-methoxyphenyl)methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**K4**),
- 5 2-[4-[2-(1-piperidyl)ethoxy]phenyl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**K5**),
2-(5-methoxy-2-pyridyl)-5-propyl-3H-imidazo[2,1-b]purin-4-one (**K6**),
2-(4-ethoxyphenyl)-5-propyl-3H-imidazo[2,1-b]purin-4-one (**K7**),
N-isopropyl-2-[4-(4-oxo-5-propyl-3H-imidazo[2,1-b]purin-2-yl)pyrazol-1-yl]acetamide (**L1**),
- 10 N-(oxetan-3-yl)-2-[4-(4-oxo-5-propyl-3H-imidazo[2,1-b]purin-2-yl)pyrazol-1-yl]acetamide (**L2**),
4-propyl-2-[1-[[3-(trifluoromethyl)phenyl]methyl]pyrazol-4-yl]-1H-imidazo[2,1-b]purin-5-one (**II**),
2-[1-(2-furylmethyl)pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**III**),
- 15 5-propyl-2-[1-(2-thienylmethyl)pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (**IV**),
2-[1-(oxazol-2-ylmethyl)pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**V**),
2-[1-(isoxazol-5-ylmethyl)pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**VI**),
2-[1-[(5-methyl-2-thienyl)methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-
- 20 4-one (**VII**),
2-[1-[(3,5-difluorophenyl)methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**VIII**),
5-propyl-2-[1-(4-pyridylmethyl)pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (**IX**),
5-propyl-2-[1-(3-pyridylmethyl)pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (**X**),
- 25 5-propyl-2-[1-(2-pyridylmethyl)pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (**XI**),
5-propyl-2-[1-(pyrimidin-5-ylmethyl)pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (**XII**),
5-propyl-2-[1-(pyridazin-4-ylmethyl)pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (**XIII**),
- 30 2-[1-[(1-oxoisindolin-5-yl)methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XIV**),

- 2-[1-[(2-methyl-1-oxo-isoindolin-5-yl)methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (XV),
- 2-[1-[(1-oxo-3,4-dihydro-2H-isoquinolin-6-yl)methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (XVI),
- 5 2-[1-[(2-oxo-3,4-dihydro-1H-quinolin-6-yl)methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (XVII),
- 5-propyl-2-[1-(quinoxalin-6-ylmethyl)pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (XVIII),
- 2-[1-(2-naphthylmethyl)pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one
10 (XIX),
- 2-[1-[[3-(azetidin-3-yl)phenyl]methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (XX),
- 2-[1-[[3-(2-methoxyethoxy)phenyl]methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (XXI),
- 15 2-[1-[[4-(2-methoxyethoxy)phenyl]methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (XXII),
- 5-propyl-2-[1-[3-[3-(trifluoromethyl)phenyl]prop-2-ynyl]pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (XXIII),
- 2-[1-[3-(3-fluorophenyl)prop-2-ynyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (XXIV),
20 b]purin-4-one (XXIV),
- 2-[1-[3-(4-fluorophenyl)prop-2-ynyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (XXV),
- 5-propyl-2-[1-[3-[4-(trifluoromethyl)phenyl]prop-2-ynyl]pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (XXVI),
- 25 2-[1-[[1-(3-fluorophenyl)-5-oxo-pyrrolidin-3-yl]methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (XXVII),
- 2-[1-[[1-(m-tolyl)-5-oxo-pyrrolidin-3-yl]methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (XXVIII),
- 2-[1-[(3-chloro-5-fluoro-phenyl)methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (XXIX),
30 b]purin-4-one (XXIX),

- 2-[[4-(4-oxo-5-propyl-3H-imidazo[2,1-b]purin-2-yl)pyrazol-1-yl]methyl]benzonitrile (**XXX**),
2-[1-[(2-fluorophenyl)methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XXXI**),
5 4-[[4-(4-oxo-5-propyl-3H-imidazo[2,1-b]purin-2-yl)pyrazol-1-yl]methyl]benzonitrile (**XXXII**),
2-[1-[[3-(4-methylpiperazin-1-yl)phenyl]methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XXXIII**),
2-[1-[1-(3-fluorophenyl)ethyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XXXIV**),
10 2-[1-[(4-isopropylphenyl)methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XXXV**),
5-propyl-2-[1-(2,2,2-trifluoroethyl)pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (**XXXVI**),
15 2-[1-(2-aminoethyl)pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XXXVII**),
5-propyl-2-(1-tetrahydropyran-4-ylpyrazol-4-yl)-3H-imidazo[2,1-b]purin-4-one (**XXXVIII**),
2-(1-cyclopentylpyrazol-4-yl)-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XXXIX**),
20 7-methyl-5-propyl-2-[1-[[3-(trifluoromethyl)phenyl]methyl]pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (**XL**),
8-methyl-5-propyl-2-[1-[[3-(trifluoromethyl)phenyl]methyl]pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (**XLI**),
7-methyl-5-propyl-2-(1-propylpyrazol-4-yl)-3H-imidazo[2,1-b]purin-4-one (**XLII**),
25 2-(1-ethylpyrazol-4-yl)-7-methyl-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XLIII**),
7-methyl-2-(1-methylpyrazol-4-yl)-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XLIV**),
5-propyl-2-(1-propylpyrazol-4-yl)-7-(trifluoromethyl)-3H-imidazo[2,1-b]purin-4-one (**XXXXV**),
30 5-propyl-7-(trifluoromethyl)-2-[1-[[3-(trifluoromethyl)phenyl]methyl]pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (**XLVI**),

2-[1-(m-tolylmethyl)pyrazol-4-yl]-4-propyl-1H-imidazo[2,1-f]purin-5-one
(XLVII),

2-[1-[(3-fluorophenyl)methyl]pyrazol-4-yl]-4-propyl-1H-imidazo[2,1-f]purin-5-one (XLVIII),

5 3-[[4-(5-oxo-4-propyl-1H-imidazo[2,1-f]purin-2-yl)pyrazol-1-yl]methyl]benzonitrile (XLIX),

3-[[4-(4-ethyl-5-oxo-1H-imidazo[2,1-f]purin-2-yl)pyrazol-1-yl]methyl]benzonitrile (L),

10 3-[1-methyl-1-[4-(4-oxo-5-propyl-3H-imidazo[2,1-b]purin-2-yl)pyrazol-1-yl]ethyl]benzonitrile (LI),

5-propyl-2-[3-[[3-(trifluoromethyl)phenyl]methoxy]isoxazol-5-yl]-3H-imidazo[2,1-b]purin-4-one (LII).

[00103] In an embodiment of the present disclosure there is provided a compound of Formula I, or its stereoisomers, pharmaceutically acceptable salts, complexes,
15 hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms and pharmaceutically active derivatives thereof for use as a medicament.

[00104] In an embodiment of the present disclosure there is provided a compound of Formula I, or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms
20 and pharmaceutically active derivatives thereof for use in treating conditions and diseases that are mediated by adenosine receptor (AR) activity.

[00105] In an embodiment of the present disclosure there is provided a compound of Formula I, or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms
25 and pharmaceutically active derivatives thereof, either alone or in combination with other therapeutic agents for use in methods for treating or lessening the severity of immunotherapies or radiotherapy or chemotherapy.

[00106] In an embodiment of the present disclosure there is provided a pharmaceutical composition comprising a compound of Formula I, or its
30 stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms and

pharmaceutically active derivative thereof together with a pharmaceutically acceptable carrier.

[00107] In an embodiment of the present disclosure there is provided a pharmaceutical composition comprising a compound of Formula I, or its
5 stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms and pharmaceutically active derivative thereof together with a pharmaceutically acceptable excipient or a pharmaceutically acceptable diluent.

[00108] In an embodiment of the present disclosure there is provided a
10 pharmaceutical composition comprising a compound of Formula I, or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms and pharmaceutically active derivative thereof together with a pharmaceutically acceptable carrier, and in combination with at least one compound and/or
15 compositions having a like therapeutic effect.

[00109] In an embodiment of the present disclosure there is provided a pharmaceutical composition comprising a compound of Formula I, or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms, and
20 pharmaceutically active derivative thereof either alone or in combination with other therapeutic agents for use in methods for treating or lessening the severity of immunotherapies or radiotherapy or chemotherapy.

[00110] In an embodiment of the present disclosure there is provided a use of compound of Formula I, or its stereoisomers, pharmaceutically acceptable salts,
25 complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms and pharmaceutically active derivative thereof, in killing or inhibiting the diseases that are mediated by adenosine receptor (AR) activity.

[00111] In an embodiment of the present disclosure there is provided a method for treatment of cancer in a subject comprising: administering to the subject an
30 effective amount of the compound of Formula I, or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers,

polymorphs, racemic mixtures, optically active forms and pharmaceutically active derivative thereof.

[00112] In an embodiment of the present disclosure there is provided a method for treatment of disorder or condition selected from melanoma, triple negative breast cancer, colon cancer, colorectal cancer, lung cancer, prostate cancer, renal cell cancer, non-small cell lung cancer, bladder cancer, cervical, vulvar or anal cancer, esophageal cancer, metastatic head and neck cancer, liver cancer, lymphoma, multiple myeloma, ovarian cancer, pancreatic cancer, acute myeloid leukemia, or Kaposi sarcoma in a subject comprising: administering to the subject an effective amount of the compound of Formula I, or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms and pharmaceutically active derivative thereof.

[00113] In an embodiment of the present disclosure there is provided a method for treatment of disorder or condition selected from melanoma, triple negative breast cancer, colon cancer, colorectal cancer, lung cancer, prostate cancer, renal cell cancer, non-small cell lung cancer, bladder cancer, cervical, vulvar or anal cancer, esophageal cancer, metastatic head and neck cancer, liver cancer, lymphoma, multiple myeloma, ovarian cancer, pancreatic cancer, acute myeloid leukemia, or Kaposi sarcoma in a subject comprising: administering to the subject an effective amount of the a pharmaceutical composition comprising a compound of Formula I, or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms, and pharmaceutically active derivative thereof.

[00114] In an embodiment of the present disclosure there is provided a pharmaceutical composition comprising compounds selected from the compound of Formula I, for the manufacture of a medicament for the treatment of a condition or disorder ameliorated by inhibition of the A_{2A}/A_{2B} receptor further comprising a therapeutically effective amount of at least one pharmaceutically acceptable excipient.

[00115] In an embodiment of the present disclosure, there is provided a process of preparation of compound of Formula I, the process is selected from Scheme 1, Scheme 2, Scheme 3, Scheme 4, or Scheme 5 as disclosed herein.

[00116] The compounds of Formula I may form stable pharmaceutically acceptable acid or base salts, and in such cases administration of a compound as a salt may be appropriate. Examples of acid addition salts include acetate, adipate, ascorbate, benzoate, benzenesulfonate, bicarbonate, bisulfate, butyrate, camphorate, camphorsulfonate, choline, citrate, cyclohexyl sulfamate, diethylenediamine, ethanesulfonate, fumarate, glutamate, glycolate, hemisulfate, 2-hydroxyethylsulfonate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, hydroxymaleate, lactate, malate, maleate, methanesulfonate, meglumine, 2-naphthalenesulfonate, nitrate, oxalate, pamoate, persulfate, phenylacetate, phosphate, diphosphate, picrate, pivalate, propionate, quinate, salicylate, stearate, succinate, sulfamate, sulfanilate, sulfate, tartrate, tosylate (p-toluenesulfonate), trifluoroacetate, and undecanoate. Examples of base salts include ammonium salts; alkali metal salts such as sodium, lithium and potassium salts; alkaline earth metal salts such as aluminum, calcium and magnesium salts; salts with organic bases such as dicyclohexylamine salts and N10 methyl-D-glucamine; and salts with amino acids such as arginine, lysine, ornithine, and so forth. Also, basic nitrogen-containing groups may be quaternized with such agents as: lower alkyl halides, such as methyl, ethyl, propyl, and butyl halides; dialkyl sulfates such as dimethyl, diethyl, dibutyl; diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl halides; arylalkyl halides such as benzyl bromide and others. Non-toxic physiologically acceptable salts are preferred, although other salts may be useful, such as in isolating or purifying the product.

[00117] In an embodiment of the present disclosure, the salts may be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water, which is removed *in vacuo* or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion-exchange resin.

- [00118] In an embodiment of the present disclosure, the compositions of the disclosure may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).
- 10 [00119] In an embodiment of the present disclosure, there is described a process of preparation of a composition comprising a compound of Formula I or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms and pharmaceutically active derivative thereof together with a carrier.
- 15 [00120] The present disclosure relates to a process of preparation of pharmaceutical composition comprising a compound of Formula I or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms and pharmaceutically active derivative thereof, together with a pharmaceutically acceptable carrier, optionally in combination with one or more other pharmaceutical compositions.
- 20 [00121] The compositions of the present disclosure may be obtained by conventional procedures using conventional pharmaceutical excipients well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents
- 25 [00122] Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate; granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl *p*-hydroxybenzoate; and anti-oxidants, such as ascorbic acid. Tablet
- 30

formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents or procedures well known in the art.

- 5 **[00123]** Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or oil such as peanut oil, liquid paraffin, or olive oil.
- 10 **[00124]** Aqueous suspensions generally contain the active ingredient in finely powdered form or in the form of nano or micronized particles together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or
- 15 condensation products of an alkylene oxide with fatty acids (for example polyoxyethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene
- 20 oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous
- 25 suspensions may also contain one or more preservatives such as ethyl or propyl p-hydroxybenzoate; anti-oxidants such as ascorbic acid); coloring agents; flavoring agents; and/or sweetening agents such as sucrose, saccharine or aspartame.
- 30 **[00125]** Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil such as arachis oil, olive oil, sesame oil or coconut oil or in a mineral oil such as liquid paraffin. The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents

such as those set out above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

5 **[00126]** Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavoring and coloring agents, may also be present.

10 **[00127]** The pharmaceutical compositions of the disclosure may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such
15 as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavoring and preservative agents.

20 **[00128]** Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavoring and/or coloring agent.

25 **[00129]** The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

30 **[00130]** Compositions for administration by inhalation may be in the form of a conventional pressurized aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used

and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

[00131] Compositions for administration may also be formulated as a liposome preparation. The liposome preparation can comprise liposomes which
5 penerate the cells of interest or stratum corneum, and fuse with the cell membrane, resulting in delivery of the contents of the liposome into the cell. Other suitable formulations can employ niosomes. Niosomes are lipid vesicles similar to liposomes, with membrane consisting largely of nonionic lipids, some forms of which are effective for transporting compounds across the stratum corneum.

10 **[00132]** Compositions for administration may also be formulated as a depot preparation, which may be administered by implantation or by intramuscular injection. The compositions may be formulated with suitable polymeric or hydrophobic material (as an emulsion in acceptable oil), ion exchange resins, or sparingly soluble derivatives.

15 **[00133]** The compound of the present disclosure can also be administered in sustained release forms or from sustained release drug delivery systems.

[00134] For further information on formulation, drug delivery as well as processing techniques the reader is referred to Remington's Pharmaceutical Sciences (21st Edition, 2005, University of the sciences in Philadelphia, Lippincott William &
20 Wilkins)

[00135] The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from
25 0.5 mg to 4 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of
30 Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990 and Remington's Pharmaceutical Sciences (21st

Edition, 2005, University of the sciences in Philadelphia, Lippincott William & Wilkins).

[00136] As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. Preferably a daily dose in the range of 1-25 mg/kg is employed. Accordingly, the optimum dosage may be determined by the practitioner who is treating any particular patient.

[00137] In any of the pharmaceutical compositions, processes, methods, uses, medicaments, and manufacturing features mentioned herein, any of the alternate aspects of the compounds of the disclosure described herein also apply.

EXAMPLES

[00138] The following examples provide the details about the synthesis, activities and applications of the compounds of the present disclosure. It should be understood the following is representative only, and that the disclosure is not limited by the details set forth in these examples.

Materials and methods:

[00139] Evaporations were carried out by rotary evaporation *in vacuo* and work up procedures were carried out after removal of residual solids by filtration; temperatures are quoted as “°C”; operations were carried out at room temperature, that is typically in the range 18 to 26 °C and without the exclusion of air unless otherwise stated, or unless the skilled person would otherwise work under an inert atmosphere; column chromatography (by the flash procedure) was used to purify compounds and was performed on Merck Kieselgel silica (Art. 9385) unless otherwise stated; in general, the course of reactions was followed by TLC, HPLC, or LC/MS and reaction times are given for illustration only; yields are given for illustration only and are not necessarily the maximum attainable; the structure of the end products of the disclosure was generally confirmed by NMR and mass spectral techniques. Proton magnetic resonance spectra were generally determined in DMSO d₆ unless otherwise stated, using a Bruker DRX 300 spectrometer or a Bruker DRX-400 spectrometer, operating at a field strength of 300 MHz or 400 MHz, respectively.

In cases where the NMR spectrum is complex, only diagnostic signals are reported. Chemical shifts are reported in parts per million downfield from tetramethylsilane as an external standard (δ scale) and peak multiplicities are shown thus: s, singlet; d, doublet; dd, doublet of doublets; dt, doublet of triplets; dm, doublet of multiplets; t, triplet; m, multiplet; br, broad. Fast atom bombardment (FAB) mass spectral data were generally obtained using a Platform spectrometer (supplied by Micromass) run in electrospray and, where appropriate, either positive ion data or negative ion data were collected or using Agilent 1100 series LC/MS equipped with Sedex 75ELSD, and where appropriate, either positive ion data or negative ion data were collected.

The lowest mass major ion is reported for molecules where isotope splitting results in multiple mass spectral peaks (for example when chlorine is present). Reverse Phase HPLC was carried out using YMC Pack ODS AQ (100x20 mmID, S 5Å particle size, 12 nm pore size) on Agilent instruments; each intermediate was purified to the standard required for the subsequent stage and was characterized in sufficient detail to confirm that the assigned structure was correct; purity was assessed by HPLC, TLC, or NMR and identity was determined by infrared spectroscopy (IR), mass spectroscopy or NMR spectroscopy as appropriate.

[00140] If not commercially available, the necessary starting materials for the procedures such as those described herein may be made by procedures which are selected from standard organic chemical techniques, techniques which are analogous to the synthesis of known, structurally similar compounds, or techniques which are analogous to the described procedure or the procedures described in the Examples.

[00141] It is noted that many of the starting materials for synthetic methods as described herein are commercially available and/or widely reported in the scientific literature or could be made from commercially available compounds using adaptations of processes reported in the scientific literature. The reader is further referred to Advanced Organic Chemistry, 5th Edition, by Jerry March and Michael Smith, published by John Wiley & Sons 2001, for general guidance on reaction conditions and reagents.

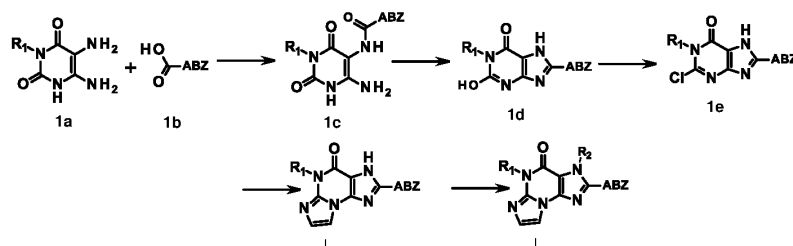
[00142] It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in compounds. The

instances where protection is necessary or desirable are known to those skilled in the art, as are suitable methods for such protection. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Greene, Protective Groups in Organic Synthesis, published by John Wiley and Sons, 1991) and as described hereinabove.

Example 1

General synthetic routes for the preparation of the compound of Formula I

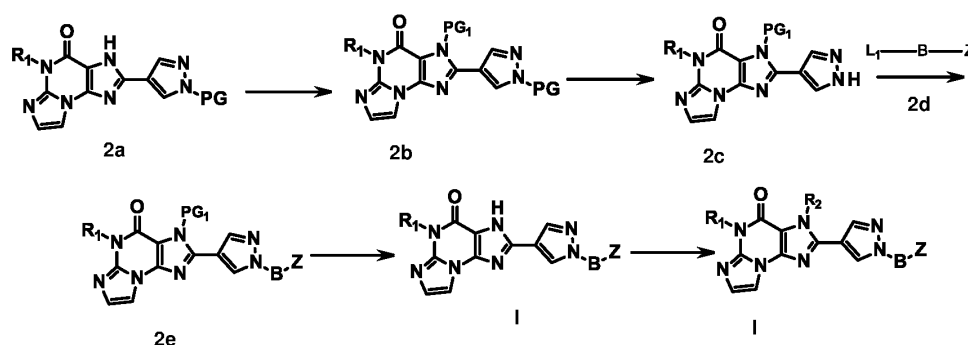
[00143] The compounds of Formula I, their tautomers, polymorphs, stereoisomers, prodrugs, solvates, pharmaceutically acceptable salts, may be prepared following independent general synthetic routes as outlined in the Schemes below:



Scheme 1

[00144] The compound of formula (1a) wherein all symbols are defined herein above, is either available commercially or may be prepared by methods well known in the art (US20080194593, Synthesis 1993, 125-128). The compound of formula (1c) can be prepared from (1a) by reaction with (1b) in presence of carbodimide, for example EDCI.HCl. Subsequently ring is closed with dehydrating reagents such as P₂O₅, NaOH to get compound (1d). The compound (1d) converted to (1e) by reaction with chlorinating reagents such as POCl₃, PCl₅, SOCl₂ and the like. The compound of formula (1e) can also be prepared directly by reaction with (1c) in presence of chlorinating reagents such as POCl₃, PCl₅, SOCl₂ and the like.

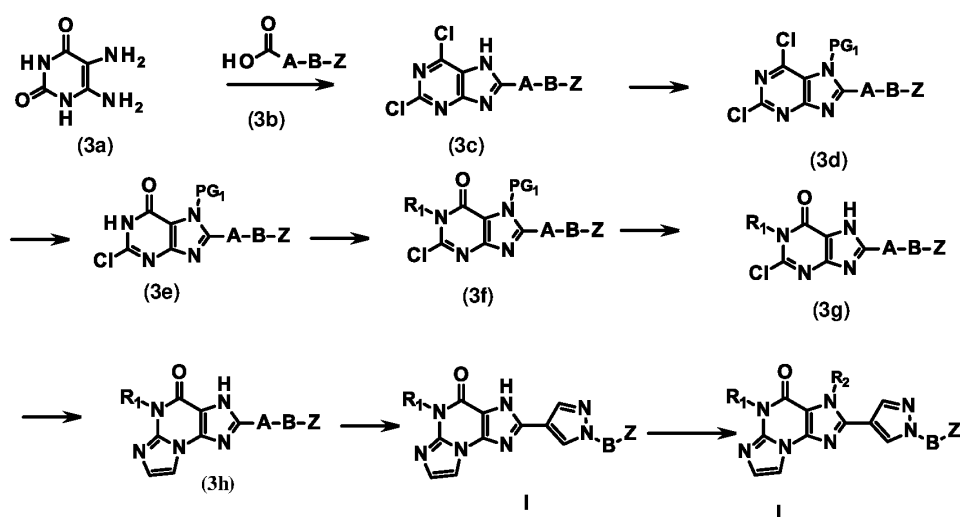
[00145] The compound of formula (1e) may be reacted with aminoacetaldehyde dimethyl acetal in presence of acid such as HCl, H₂SO₄, AcOH and the like, to obtain compound of formula (1), which is reacted with R²-L to provide the compound of Formula I.



Scheme 2

[00146] The compound of formula (2a) wherein PG is protecting group, such as benzyl and the like prepared by using scheme 1.

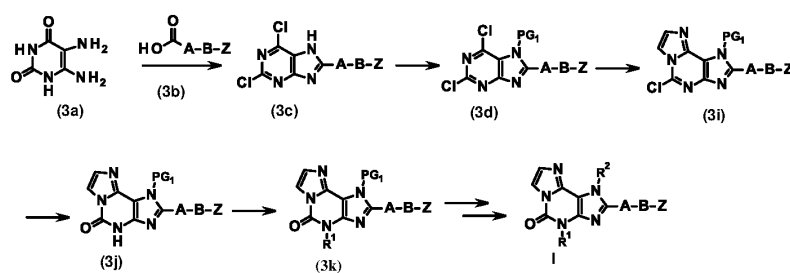
- 5 [00147] The compound of formula (2b) may be prepared from compound of formula (2a) by protection of $-NH$ wherein PG_1 may be SEM, and the like. The compound of formula (2b) can be converted to a formula (2c) by deprotection. The compound of formula (2c) reacted with (2d) where in L_1 is leaving group and B and Z are defined above to provide compound of formula (2e) followed by deprotection
- 10 to provide compound (I). Compounds of Formula I may further be reacted with R^2-L to provide compounds of Formula I wherein R^2 is other than hydrogen and is as defined herein above.



Scheme 3

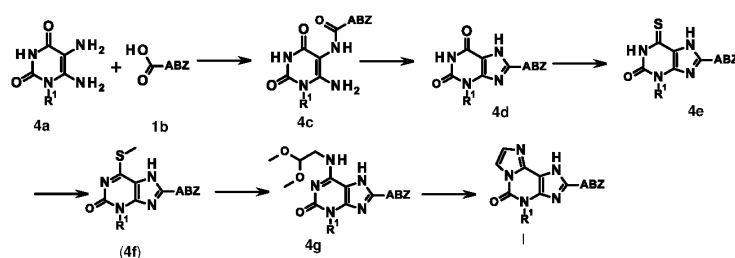
[00148] The compound of formula (3a) wherein all symbols are defined herein above is available commercially. Compound (3a) can be reacted with acid (3b) in presence of POCl₃ to get compound of formula (3c) which is further reacted with protecting groups to provide compound (3d).

5 [00149] The compound of formula (3d) can be converted to a formula (3e) by hydrolyzing with bases like K₂CO₃ or Na₂CO₃ or Cs₂CO₃ and the like in presence of inert solvents like CH₃CN or EtOH or THF and the like. The compound of formula (3e) can be converted to a formula (3f) by reaction with R¹-Hal wherein R¹ is defined above and followed by deprotection to provide compound (3g). Then
10 compound (I) can be obtained in a similar way as described above.



Scheme 4

[00150] The compound of formula (3d) can be obtained in a similar way as described above. The compound of formula (3d) can be converted to a formula (3i) by reaction with aminoacetaldehyde dimethyl acetal in presence of base like Et₃N, DIPEA and the like and followed by reaction with acid such as HCl, H₂SO₄, AcOH and the like. The compound of formula (3i) can be converted to a formula (3j) by hydrolyzing with bases like K₂CO₃ or Na₂CO₃ or Cs₂CO₃ and the like in presence of inert solvents like CH₃CN or EtOH or THF and the like. The compound of formula
15 (3j) can also be synthesized from (3i) by reaction with acid such as HCl, H₂SO₄, AcOH and the like. The compound of formula (3j) can be converted to a formula (3k) by reaction with R¹-Hal wherein R¹ is defined above and followed by deprotection to provide compound (I).
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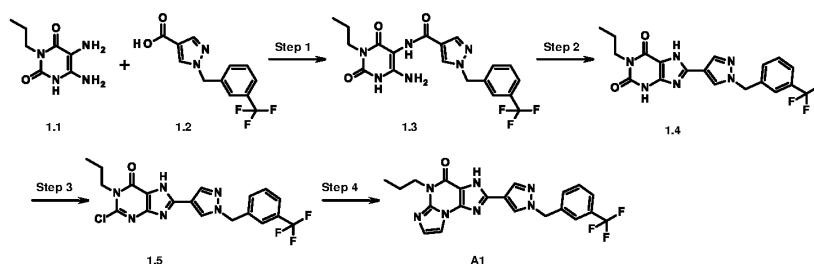
[00151] The compound of formula (4a) wherein all symbols are defined herein above, is either available commercially or may be prepared by methods well known in the art (WO2009157938, US 20130324724). The compound of formula (4d) can be obtained in a similar way as described above. The compound of formula (4e) can be obtained from (4d) by reaction with P₄S₁₀ and followed by alkylation to obtained (4f). The compound of formula (4f) can be converted to a formula (4g) by reaction with aminoacetaldehyde dimethyl acetal in presence of base like Et₃N, DIPEA and the like and followed by reaction with acid such as HCl, H₂SO₄, AcOH and the like to obtain compound of Formula I.

[00152] Wherever desired or necessary, in any of the above-mentioned processes, functional groups may be transformed to different functional groups such as an ester function being converted to an acid, amide, hydroxymethyl, keto, aldehyde as well as an ester. The said conversions may be carried out using reagents and conditions well documented in the literature.

[00153] Wherever desired or necessary, in any of the above-mentioned processes, any of the compounds of Formula I may be converted into a pharmaceutically acceptable salt or vice versa or converting one salt form into another pharmaceutically acceptable salt form.

Example 2

Example A1: 5-propyl-2-[1-[[3-(trifluoromethyl)phenyl]methyl]pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one



Step 1: Synthesis of N-(6-amino-2,4-dioxo-3-propyl-1H-pyrimidin-5-yl)-1-[[3-(trifluoromethyl)phenyl]methyl]pyrazole-4-carboxamide

A mixture of **1.1** (30 g, 163.04 mmol), **1.2** (44.0 g, 163.04 mmol) in methanol (1500 mL) were cooled to 0 °C and added EDCI.HCl (37.5 g, 195.65 mmol). The reaction mixture was stirred at 25 °C for 16 hours. Reaction completion was confirmed by TLC, and the organic volatiles were evaporated. To this residue water (2000 mL) was added and the precipitate was filtered off, and washed with cold water (500 mL), washed with n-hexane dried to obtain **1.3** as a pale yellow solid. (60.0 g, 84 %).

ESI-MS(m/z): 437.2 (M + 1); ¹H NMR (400 MHz, DMSO-d₆): δ 0.82 (t, J = 7.6 Hz, 3H); 1.46-1.51 (m, 2H); 3.64 (t, J = 7.6 Hz, 2H); 5.49 (s, 2H); 6.01 (s, 2H); 7.55-7.68 (m, 2H); 7.68-7.70 (m, 2H); 7.99 (s, 1H); 8.37 (s, 1H); 8.55 (s, 1H); 10.42 (s, 1H).

Step 2: Synthesis of 1-propyl-8-[1-[[3-(trifluoromethyl)phenyl]methyl]pyrazol-4-yl]-3,7-dihydropurine-2,6-dione

In a mixture of **1.3** (60 g, 137.6 mmol) and DMF (600 mL), added P₂O₅ (68.4 g, 481.6 mmol) portion wise and heated at 100 °C for 30 minutes. Reaction completion was confirmed by TLC, and mixture was cooled to 20-25 °C. The reaction mixture was slowly poured into water (2.5 L) with vigorous stirring. Solid material separated was filtered off, and washed with cold water (500 mL), washed with n-hexane dried to obtain **1.4** as a pale yellow solid (53 g, 93 %).

ESI-MS(m/z): 419.2 (M + 1); ¹H NMR (400 MHz, DMSO-d₆): δ 0.87 (t, J = 7.2 Hz, 3H); 1.53-1.60 (m, 2H); 3.98 (t, J = 7.2 Hz, 2H); 5.53 (s, 2H); 7.57-7.64 (m, 2H); 7.69-7.71 (m, 2H); 8.08 (s, 1H); 8.47 (s, 1H); 11.83 (s, 1H); 13.39 (br s, 1H).

Step 3: Synthesis of 2-chloro-1-propyl-8-[1-[[3-(trifluoromethyl)phenyl]methyl]pyrazol-4-yl]-7H-purin-6-one

A mixture of **1.4** (35 g, 83.93 mmol), NH₄Cl (44.8 g, 83.7 mmol) and POCl₃ (1000 mL) were heated at 120-125 °C for 72 h. Reaction completion was confirmed by TLC, mixture was cooled to 20-25 °C. It was then concentrated under vacuo and quenched with cold water slowly and solid material was separated. It was filtered off and washed with cold water, dried under vacuo. The crude product was purified by column chromatography using silica gel (230-400 mesh) and 0.5 to 4 % methanol in chloroform as an eluent to obtain **1.5** as a pale yellow solid. (17 g, 47 %)

ESI-MS(m/z): 437.1 (M + 1); ¹H NMR (400 MHz, CD₃OD): δ 1.02 (t, *J* = 7.2 Hz, 3H); 1.72-1.84 (m, 2H); 4.29 (t, *J* = 7.6 Hz, 2H); 5.52 (s, 2H); 7.56-7.57 (m, 2H); 7.61-7.63 (m, 2H); 8.12 (s, 1H); 8.35 (s, 1H)

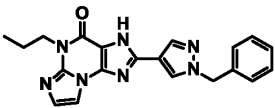
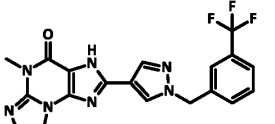
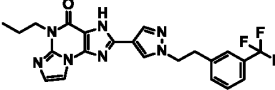
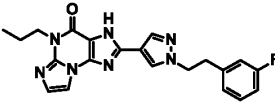
Step 4: Synthesis of 5-propyl-2-[1-[[3-(trifluoromethyl)phenyl]methyl]pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one

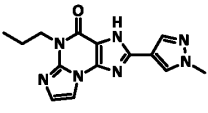
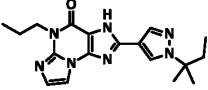
To a solution of **1.5** (0.2 g, 0.46 mmol) in NMP (5 mL) was added DIPEA (0.30 mL, 1.83 mmol), and aminoacetaldehyde dimethyl acetal (0.20 mL, 1.83 mmol). The mixture was stirred at 130°C for 3 days. Reaction completion was confirmed by TLC, then cooled to room temperature and residue was dissolved in water (50 mL), and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layer was washed with brine (20 mL), dried over Na₂SO₄ and concentrated under vacuo to obtain a crude product. It was purified by combiflash column chromatography using 2-5 % methanol in DCM as a mobile phase to obtain the title compound **A1** as a white solid (0.075 g, 37%).

MS(ESI)m/z: 442.2 (M + 1); ¹H NMR (400 MHz, DMSO-d₆): δ 0.90 (t, *J* = 7.2 Hz, 3H); 1.71-1.74 (m, 2H); 4.13-4.16 (m, 2H); 5.52 (s, 2H); 7.15 (d, *J* = 1.2 Hz, 1H); 7.59-7.69 (m, 5H); 8.16 (s, 1H); 8.55 (s, 1H); 13.80 (br s, 1H).

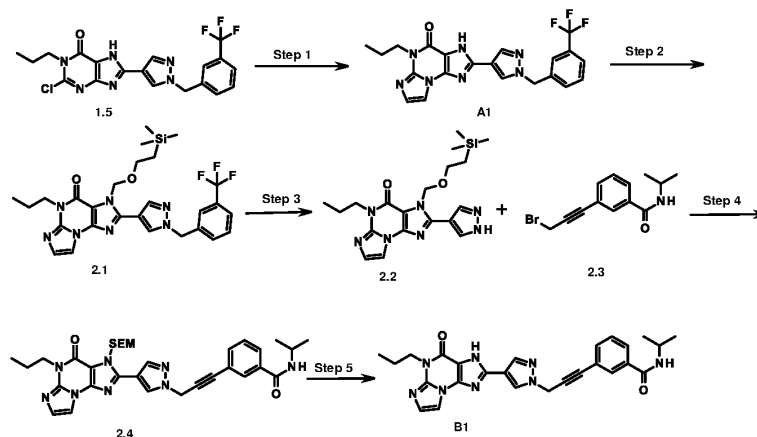
Following examples as shown in Table were prepared according to similar sequence of procedures as used for the synthesis of **Example A1**

Ex.No.	Structure	IUPAC Name ¹ H NMR (400 MHz) data	MS(ESI)m/z: (M+1)
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A2	 2-(1-benzylpyrazol-4-yl)-5-propyl-3H-imidazo[2,1-b]purin-4-one	DMSO- <i>d</i> ₆ : δ 0.92 (t, J = 7.2 Hz, 3H); 1.71-1.76 (m, 2H); 4.17 (t, J = 7.2 Hz, 2H); 5.42 (s, 2H); 7.16 (d, J = 1.6 Hz, 1H); 7.31-7.34 (m, 3H); 7.36-7.38 (m, 2H); 7.68 (d, J = 1.2 Hz, 1H); 8.15 (s, 1H); 8.49 (s, 1H); 13.86 (br s, 1H).	374.2
A3	 5-methyl-2-[1-[[3-(trifluoromethyl)phenyl]methyl]pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one	DMSO- <i>d</i> ₆ : δ 3.58 (s, 3H); 5.53 (s, 2H); 7.13 (d, J = 1.6 Hz, 1H); 7.60-7.65 (m, 3H); 7.69-7.71 (m, 2H); 8.11 (s, 1H); 8.50 (s, 1H)	414.1
A4	 5-propyl-2-[1-[2-[3-(trifluoromethyl)phenyl]ethyl]pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one	DMSO- <i>d</i> ₆ : δ 0.92 (t, J = 7.2 Hz, 3H); 1.71-1.77 (m, 2H); 3.24-3.26 (m, 2H); 4.15-4.19 (m, 2H); 4.48 (t, J = 7.2 Hz, 2H); 7.16 (s, 1H); 7.46-7.57 (m, 4H); 7.663-7.666 (m, 1H); 8.14 (s, 1H); 8.30 (s, 1H); 13.83 (br s, 1H).	456.2
A5	 2-[1-[2-(3-fluorophenyl)ethyl]pyr	DMSO- <i>d</i> ₆ : δ 0.92 (t, J = 8.0 Hz, 3H); 1.71-1.77 (m, 2H); 3.17 (t, J = 7.2 Hz, 2H); 4.17 (t, J = 8.0 Hz, 2H); 4.46 (t, J = 7.2 Hz, 2H); 6.99-7.02 (m, 2H); 7.04-7.07 (m, 1H); 7.16 (d, J = 1.2 Hz, 1H);	406.2

	azol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one	7.27-7.33 (m, 1H); 7.66 (d, $J = 1.6$ Hz, 1H); 8.13 (s, 1H); 8.30 (s, 1H); 13.83 (br s, 1H).	
A6	 2-(1-methylpyrazol-4-yl)-5-propyl-3H-imidazo [2,1-b] purin-4-one	DMSO-d ₆ : δ 0.92 (t, $J = 8.0$ Hz, 3H); 1.74-1.76 (m, 2H); 3.92 (s, 3H); 4.18 (t, $J = 7.2$ Hz, 2H); 7.17 (s, 1H); 7.68 (s, 1H); 8.09 (s, 1H); 8.37 (s, 1H); 13.85 (s, 1H).	298.2
A7	 2-[1-(1,1-dimethylpropyl)pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one	DMSO-d ₆ : δ 0.64 (t, $J = 7.6$ Hz, 3H); 0.92 (t, $J = 7.6$ Hz, 3H); 1.55 (s, 6H); 1.72-1.78 (m, 2H); 1.84-1.90 (m, 2H); 4.17 (t, $J = 7.6$ Hz, 2H); 7.16 (d, $J = 1.6$ Hz, 1H); 7.68 (d, $J = 1.6$ Hz, 1H); 8.13 (s, 1H); 8.46 (s, 1H); 12.83 (br s, 1H).	354.3

Example B1: N-isopropyl-3-[3-[4-(4-oxo-5-propyl-3H-imidazo[2,1-b]purin-2-yl)pyrazol-1-yl]prop-1-ynyl]benzamide



Step 1: Synthesis of 5-propyl-2-[1-[[3-(trifluoromethyl)phenyl]methyl]pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one

To a solution of **1.5** (9.0 g, 20.64 mmol) in NMP (45 mL) was added DIPEA (3.4 mL, 20.64 mmol), and aminoacetaldehyde dimethyl acetal (8.9 mL, 82.56 mmol). The mixture was stirred at 130°C for 6 hours then reaction mixture was cooled to room temperature then added conc. HCl (27 mL) and stirred at 130 °C for 16 hours. Reaction completion was confirmed by TLC then cooled to room temperature and residue was dissolved in water (500 mL), and the mixture was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄ and concentrated under vacuo to obtain a crude product. To the residue added cold methanol solid obtained was filtered and washed with n-hexane and dried to obtain **A1** as a white solid (6.0 g, 66%).

MS(ESI)m/z: 442.2 (M + 1); ¹H NMR (400 MHz, DMSO-d₆): δ 0.90 (t, *J* = 7.2 Hz, 3H); 1.71-1.74 (m, 2H); 4.13-4.16 (m, 2H); 5.52 (s, 2H); 7.15 (d, *J* = 1.2 Hz, 1H); 7.59-7.69 (m, 5H); 8.16 (s, 1H); 8.55 (s, 1H); 13.80 (br s, 1H).

Step 2: Synthesis of 5-propyl-2-[1-[[3-(trifluoromethyl)phenyl]methyl]pyrazol-4-yl]-3-(2 trimethylsilylethoxymethyl)imidazo[2,1-b]purin-4-one

To a solution of **A1** (5.0 g, 11.33 mmol) in DMF (50 mL) was added K₂CO₃ (7.8 g, 56.70 mmol), and 2-(chloromethoxy)ethyl-trimethyl-silane (20 mL, 113.37 mmol). The mixture was stirred at room temperature for 2 days. Reaction completion was confirmed by TLC then dissolved in water (500 mL), and the mixture was extracted

with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄ and concentrated under vacuo to obtain a crude product. The residue was purified by column chromatography using 30-35 % ethyl acetate in hexane as a mobile phase to obtain the title compound **2.1** as a white solid (6.0 g, 93%).

MS(ESI)m/z: 572.0 (M + 1); ¹H NMR (400 MHz, DMSO-d₆): δ -0.13 (s, 9H), 0.83-0.92 (m, 5H); 1.71-1.77 (m, 2H); 3.67-3.71 (m, 2H); 4.18 (t, *J* = 6.8 Hz, 2H); 5.58 (s, 2H); 5.94 (s, 2H); 7.18 (d, *J* = 1.6 Hz, 1H); 7.33-7.37 (m, 1H); 7.61-7.63 (m, 1H); 7.68-7.71 (m, 3H); 8.11 (s, 1H); 8.60 (s, 1H).

Step 3: Synthesis of 5-propyl-2-(1H-pyrazol-4-yl)-3-(2-trimethylsilylethoxymethyl)imidazo[2,1-b]purin-4-one

To a solution of **2.1** (1.6 g, 2.84 mmol) in THF (2 mL) was added potassium tert butoxide (2.55 g, 22.76 mmol), and DMSO (2.3 g, 22.76 mmol). The mixture was cooled to °C and Oxygen was bubbled for 30 minutes. Reaction completion was confirmed by TLC then quenched with aqueous saturated solution of ammonium chloride (4 mL) at 0°C extracted with ethyl acetate(150 mL), washed with water(30 mL), brine (30 mL), dried over Na₂SO₄ and concentrated under vacuo to obtain **2.2** as an Off white solid (1.1 g, 94%).

MS(ESI)m/z: 414.3; ¹H NMR (400 MHz, DMSO-d₆): δ -0.087 (s, 9H), 0.86-0.93 (m, 5H); 1.72-1.78 (m, 2H); 3.70-3.74 (m, 2H); 4.19 (t, *J* = 7.2 Hz, 2H); 5.94 (s, 2H); 7.19 (d, *J* = 1.6 Hz, 1H); 7.74 (d, *J* = 1.6 Hz, 1H); 8.10 (s, 1H); 8.39 (s, 1H); 13.52 (br s, 1H).

Step 4: Synthesis of N-isopropyl-3-[3-[4-[4-oxo-5-propyl-3-(2-trimethylsilylethoxymethyl)imidazo[2,1-b]purin-2-yl]pyrazol-1-yl]prop-1-ynyl]benzamide (2.4).

Synthesis of 3-iodo-N-isopropyl-benzamide

A mixture of 3-iodobenzoic acid (3.0 g, 12.09 mmol), isopropyl amine (1.2 mL, 14.51 mmol) in DMF (30 mL) were cooled to 0 °C and added EDCI.HCl (3.25 g, 16.93 mmol). The reaction mixture was stirred at 25 °C for 16 hours. Reaction completion was confirmed by TLC, residue was dissolved in water (150 mL), and

the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated under vacuo to obtain a crude product. The residue was purified by combiflash column chromatography using 10-15 % ethyl acetate in hexane as a mobile phase to obtain

5 the title compound 3-iodo-N-isopropyl-benzamide as white solid (1.0 g, 28 %).

MS(ESI)m/z: 289.9 (M + 1); ¹H NMR (400 MHz, DMSO-d₆): δ 1.15 (d, J = 6.4 Hz, 6H); 4.05-4.10 (m, 1H); 7.26 (d, J = 8.0 Hz, 1H); 7.83-7.88 (m, 2H); 8.18 (d, J = 2.0 Hz, 1H); 8.29-8.32 (m, 1H).

Synthesis of 3-(3-hydroxyprop-1-ynyl)-N-isopropyl-benzamide

10 A mixture of propargyl alcohol (0.26 mL, 4.15 mmol), 3-iodo-N-isopropyl-benzamide (1.0 g, 3.46 mmol), copper iodide (0.02 g, 0.1 mmol), dichlorobis (triphenylphosphine) palladium (II) (0.12 g, 0.17 mmol), 1,4-dioxane:triethylamine (1:1)(20ml) was degassed for 10min. and stirred for 2 hours at 60 °C. Reaction completion was confirmed by TLC, residue was concentrated under vacuo to obtain

15 a crude product. The residue was purified by combiflash column chromatography using 15-20 % ethyl acetate in hexane as a mobile phase to obtain the title compound 3-(3-hydroxyprop-1-ynyl)-N-isopropyl-benzamide as white solid (0.5 g, 67 %).

MS(ESI)m/z: 218.0 (M + 1); ¹H NMR (400 MHz, DMSO-d₆): δ 1.00 (d, J = 6.4 Hz, 6H); 4.02-4.04 (m, 1H); 4.33 (d, J = 5.6 Hz, 2H); 5.36 (t, J = 5.6 Hz, 1H); 7.46 (t, J = 7.6 Hz, 1H); 5.54-7.55 (m, 1H); 7.83 (d, J = 7.6 Hz, 1H); 7.92 (s, 1H); 8.30-8.40 (m, 1H).

20

Synthesis of 3-(3-bromoprop-1-ynyl)-N-isopropyl-benzamide

A mixture of 3-(3-hydroxyprop-1-ynyl)-N-isopropyl-benzamide (0.5 g, 2.30 mmol), and DCM (10 mL) was cooled to 0 °C added tribromo phosphine (0.11 mL, 1.15 mmol) slowly and stirred at room temperature for 1 hour. Reaction completion was confirmed by TLC, reaction mixture was quenched with saturated NaHCO₃ solution and extracted with DCM (3 x 15 mL), washed with saturated brine solution, dried over Na₂SO₄, and evaporated under vacuo to obtain 3-(3-bromoprop-1-ynyl)-N-isopropyl-benzamide as a white solid (**2.3**) (0.55 g, 86%).

25

MS(ESI)m/z: 279.9 & 282.9 (M + 1); ¹H NMR (400 MHz, DMSO-d₆): δ 1.27 (d, *J* = 6.4 Hz, 6H); 4.16 (s, 2H); 4.25-4.29 (m, 1H); 5.88 (br s, 1H); 7.39 (t, *J* = 8.0 Hz, 1H); 7.53-7.55 (m, 1H); 7.74-7.78 (m, 2H).

Synthesis of N-isopropyl-3-[3-[4-[4-oxo-5-propyl-3-(2-trimethylsilylethoxymethyl)imidazo[2,1-b]purin-2-yl]pyrazol-1-yl]prop-1-ynyl]benzamide (2.4)

To a solution **2.2** (0.1 g, 0.24 mmol) in acetone (10 mL) was added potassium carbonate (0.05 g, 0.36 mmol), and **2.3** (0.081 g, 0.29 mmol). The mixture was stirred at 60 °C for 2 days. Reaction completion was confirmed by TLC then cooled to room temperature and filtered through celite pad, washed with acetone (15 mL) and concentrated under vacuo to obtain a crude product. The residue was purified by combiflash column chromatography using 2-5 % methanol in DCM as a mobile phase to give the title compound **2.4** as a white solid (0.14 g, 95%).

MS(ESI)m/z: 613.0 (M + 1); ¹H NMR (400 MHz, DMSO-d₆): δ -0.099 (s, 9H), 0.83-0.95 (m, 5H); 1.12-1.16 (m, 6H); 1.72-1.78 (m, 2H); 3.72 (t, *J* = 8.4 Hz, 2H); 4.05-4.10 (m, 1H); 4.20 (t, *J* = 6.8 Hz, 2H); 5.49 (s, 2H); 5.95 (s, 2H); 7.20 (d, *J* = 1.6 Hz, 1H); 7.46-7.50 (m, 1H); 7.60-7.62 (m, 1H); 7.75 (d, *J* = 1.6 Hz, 1H); 7.76-7.89 (m, 1H); 7.96 (d, *J* = 1.6 Hz, 1H); 8.15 (s, 1H); 8.33 (d, *J* = 7.2 Hz, 1H); 8.58 (s, 1H).

Step 5: Synthesis of N-isopropyl-3-[3-[4-(4-oxo-5-propyl-3H-imidazo[2,1-b]purin-2-yl]pyrazol-1-yl]prop-1-ynyl]benzamide

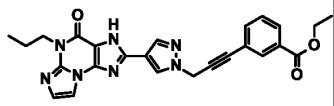
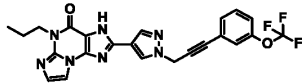
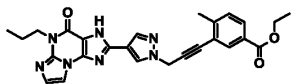
A solution of **2.4** (0.14 g, 0.23 mmol) in ethanol, 2N HCl (10 mL) was heated at 80°C for 8 hours. Reaction completion was confirmed by TLC then cooled to room temperature and concentrated under vacuo to obtain a crude product. The residue was basified by aqueous NaHCO₃ solution up to PH (7-8) then solid obtained was filtered, washed with n-hexane, dried and purified by combiflash column chromatography using 2-5 % methanol in DCM as a mobile phase to give the title compound **B1** as a white solid (0.060 g, 54%).

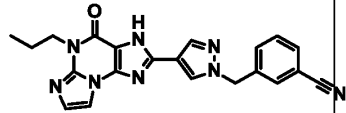
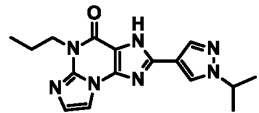
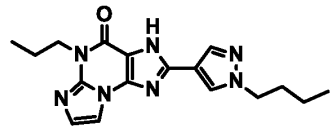
MS(ESI)m/z: 483.3 (M + 1); ¹H NMR (400 MHz, DMSO-d₆): δ 0.92 (t, *J* = 7.2 Hz, 3H); (1.15 (d, *J* = 6.4 Hz, 6H), 1.72-1.78 (m, 2H); 4.05-4.11 (m, 1H); 4.18 (t, *J* = 7.6 Hz, 2H); 5.45 (s, 2H); 7.17 (d, *J* = 1.6 Hz, 1H); 7.47-7.52 (m, 1H); 7.64 (d, *J* = 7.6

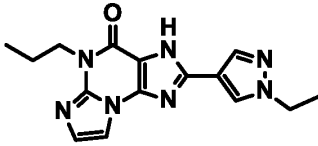
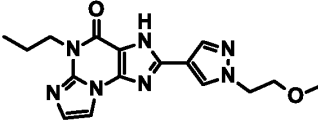
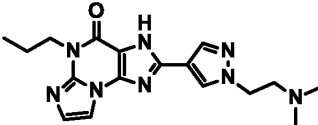
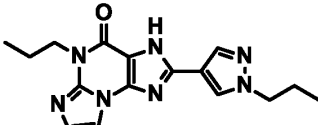
Hz, 1H); 7.71 (d, $J = 1.6$ Hz, 1H); 7.88 (d, $J = 8.0$ Hz, 1H); 7.97 (br s, 1H); 8.19 (s, 1H); 8.34 (d, $J = 7.6$ Hz, 1H); 8.60 (s, 1H); 13.95 (br s, 1H).

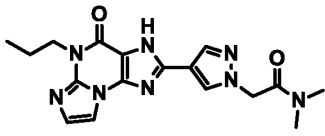
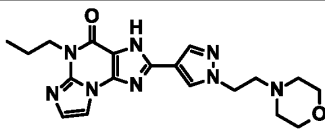
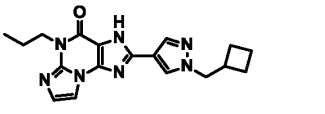
Following examples as shown in Table were prepared according to similar sequence

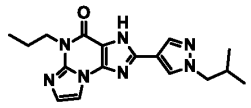
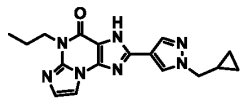
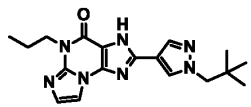
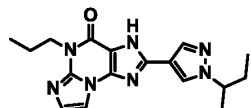
5 of procedures as used for the synthesis of **Example B1**

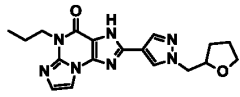
Ex. No.	Structure IUPAC Name	¹ H NMR(400 MHz) data	MS(ESI) ^{m/z} : (M+1)
B2	 Ethyl 3-[3-[4-(4-oxo-5-propyl-3H-imidazo[2,1-b]purin-2-yl)pyrazol-1-yl]prop-1-ynyl]benzoate	DMSO-d ₆ : δ 0.92 (t, $J = 7.6$ Hz, 3H); 1.32 (t, $J = 7.2$ Hz, 3H); 1.72-1.78 (m, 2H); 4.18 (t, $J = 7.6$ Hz, 2H); 4.33 (t, $J = 6.8$ Hz, 2H); 5.45 (s, 2H); 7.17 (d, $J = 1.6$ Hz, 1H); 7.58 (dd, $J = 7.6, 8.0$ Hz, 1H); 7.71 (d, $J = 1.2$ Hz, 1H); 7.78 (d, $J = 7.6$ Hz, 1H); 7.98-8.01 (m, 2H); 8.19 (s, 1H); 8.61 (s, 1H); 13.98 (br s, 1H)	470.2
B3	 5-propyl-2-[1-[3-[3-(trifluoromethoxy)phenyl]prop-2-ynyl]pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one	DMSO-d ₆ : δ 0.92 (t, $J = 7.6$ Hz, 3H); 1.72-1.78 (m, 2H); 4.18 (t, $J = 7.2$ Hz, 2H); 5.45 (s, 2H); 7.17 (d, $J = 1.6$ Hz, 1H); 7.46 (br s, 1H); 7.51 (br s, 1H); 7.55-7.56 (m, 2H); 7.70 (d, $J = 1.6$ Hz, 1H); 8.19 (s, 1H); 8.59 (s, 1H); 13.95 (br s, 1H)	482.2
B6		DMSO-d ₆ : δ 0.92 (t, $J = 7.2$ Hz, 3H); 1.31 (t, $J = 7.2$ Hz, 3H); 1.72-1.78 (m, 2H); 2.32 (s, 3H); 4.18 (t, $J = 7.6$ Hz, 2H); 4.30 (t, $J = 6.8$ Hz, 2H); 5.48 (s,	484.2

	Ethyl 4-methyl-3-[3-[4-(4-oxo-5-propyl-3H-imidazo[2,1-b]purin-2-yl)pyrazol-1-yl]prop-1-ynyl]benzoate	2H); 7.17 (d, $J = 1.6$ Hz, 1H); 7.48 (d, $J = 7.6$ Hz, 1H); 7.70 (d, $J = 1.6$ Hz, 1H); 7.88 (dd, $J = 2.0, 8.0$ Hz, 1H); 7.96 (d, $J = 1.6$ Hz, 1H); 8.19 (s, 1H), 8.61 (s, 1H); 13.95 (br s, 1H)	
B7	 3-[[4-(4-oxo-5-propyl-3H-imidazo[2,1-b]purin-2-yl)pyrazol-1-yl]methyl]benzonitrile	DMSO- d_6 : δ 0.92 (t, $J = 7.2$ Hz, 3H); 1.70-1.76 (m, 2H); 4.17 (t, $J = 6.8$ Hz, 2H); 5.50 (s, 2H); 7.22 (s, 1H); 7.60-7.63 (m, 2H); 7.72 (s, 1H); 7.81 (s, 2H); 8.18 (s, 1H); 8.56 (s, 1H); 13.91 (br s, 1H).	399.2
B8	 2-(1-isopropylpyrazol-4-yl)-5-propyl-3H-imidazo[2,1-b]purin-4-one	DMSO- d_6 : δ 0.92 (t, $J = 7.6$ Hz, 3H); 1.46 (d, $J = 6.8$ Hz, 6H); 1.72-1.78 (m, 2H); 4.17 (t, $J = 7.6$ Hz, 2H); 4.58 (m, 1H); 7.17 (d, $J = 1.6$ Hz, 1H); 7.67 (d, $J = 1.6$ Hz, 1H); 8.12 (s, 1H); 8.45 (s, 1H); 13.92 (br s, 1H)	326.2
B9	 2-(1-butylpyrazol-4-yl)-5-propyl-3H-imidazo[2,1-b]purin-4-one	DMSO- d_6 : δ 0.88-0.94 (m, 5H); 1.23-1.29 (m, 3H); 1.74-1.80 (m, 4H); 4.15-4.20 (m, 4H); 7.16 (d, $J = 1.6$ Hz, 1H); 7.67 (s, 1H); 8.10 (s, 1H); 8.40 (s, 1H); 13.86 (br s, 1H)	340.2

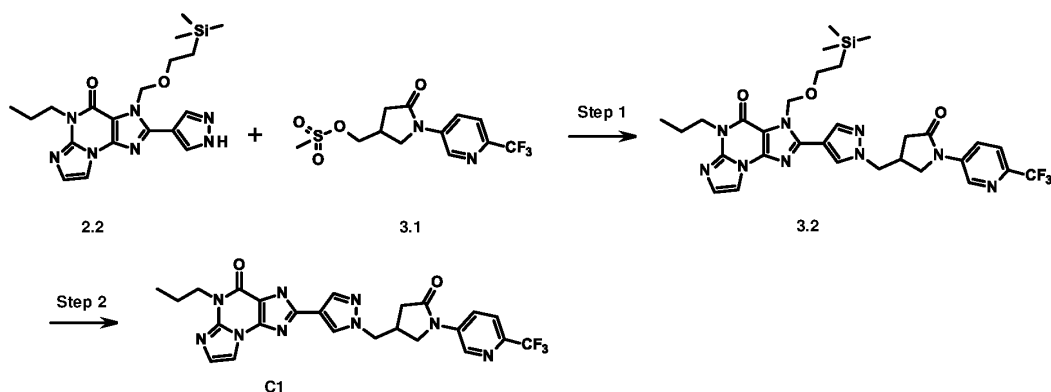
B10	 2-(1-ethylpyrazol-4-yl)-5-propyl-3H-imidazo[2,1-b]purin-4-one	DMSO-d ₆ : δ 0.94 (t, J = 7.2 Hz, 3H); 1.42 (t, J = 7.2 Hz, 3H); 1.71-1.77 (m, 2H); 4.15-4.25 (m, 4H); 7.34 (br s, 1H); 7.79 (br s, 1H); 8.12 (d, J = 0.8 Hz, 1H); 8.43 (s, 1H); 13.95 (br s, 1H).	312.2
B11	 2-[1-(2-methoxyethyl)pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one	DMSO-d ₆ : δ 0.94 (t, J = 7.6 Hz, 3H); 1.72-1.77 (m, 2H); 3.26 (s, 3H); 3.72 (t, J = 4.8 Hz, 2H); 4.18 (t, J = 7.2 Hz, 2H); 4.36 (t, J = 4.8 Hz, 2H); 7.33 (br s, 1H); 7.81 (s, 1H); 8.13 (s, 1H); 8.41 (s, 1H); 13.99 (s, 1H)	342.2
B12	 2-[1-(2-dimethylaminoethyl)pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one	DMSO-d ₆ : δ 0.96 (t, J = 7.2 Hz, 3H); 1.71-1.77 (m, 2H); 2.76 (s, 3H); 2.78 (s, 3H); 3.59-3.63 (m, 2H); 4.21 (t, J = 8.0 Hz, 2H); 4.72 (t, J = 6.4 Hz, 2H); 7.56 (s, 1H); 7.94 (d, J = 1.6 Hz, 1H); 8.26 (s, 1H); 8.58 (s, 1H); 14.32 (br s, 1H)	355.3
B13	 5-propyl-2-(1-ethylpyrazol-4-yl)-3H-imidazo[2,1-b]purin-4-one	DMSO-d ₆ : δ 0.85 (t, J = 7.6 Hz, 3H); 0.92 (t, J = 7.2 Hz, 3H); 1.74-1.78 (m, 2H); 1.80-1.84 (m, 2H); 4.13-4.20 (m, 4H); 7.17 (d, J = 1.6 Hz, 1H); 7.68 (d, J = 0.8 Hz, 1H); 8.13 (s, 1H); 8.41 (s, 1H); 13.84 (br s, 1H).	326.2

	propylpyrazol-4-yl)-3H-imidazo[2,1-b]purin-4-one		
B14	 N,N-dimethyl-2-[4-(4-oxo-5-propyl-3H-imidazo[2,1-b]purin-2-yl)pyrazol-1-yl]acetamide	DMSO-d₆: δ 0.93 (t, J = 7.6 Hz, 3H); 1.75 (q, J = 7.2 Hz, 2H); 2.87 (s, 3H); 3.05 (s, 3H); 4.18 (t, J = 7.2 Hz, 2H); 5.22 (s, 2H); 7.17 (d, J = 1.6 Hz, 1H); 7.06 (d, J = 1.6 Hz, 1H); 8.10 (s, 1H); 8.33 (s, 1H); 13.90 (br s, 1H).	369.0
B15	 2-[1-(2-morpholinoethyl)pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one	DMSO-d₆: δ 0.97 (t, J = 7.2 Hz, 3H); 1.71-1.76 (m, 2H); 3.13-3.16 (m, 2H); 3.36-3.39 (m, 2H); 3.64-3.67 (m, 2H); 3.80-3.86 (m, 2H); 3.94-3.96 (m, 2H); 4.23 (t, J = 7.6 Hz, 2H); 4.80 (t, J = 6.8 Hz, 2H); 7.68 (s, 1H); 8.09 (s, 1H); 8.26 (s, 1H); 8.59 (s, 1H); 14.2 (br s, 1H)	397.2
B16	 2-[1-(cyclobutylmethyl)pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one	DMSO-d₆: δ 0.93 (t, J = 7.2 Hz, 3H); 1.71-1.90 (m, 6H); 1.97-2.01 (m, 2H); 2.76-2.82 (m, 1H); 4.15-4.22 (m, 4H); 7.31 (br s, 1H); 7.78 (br s, 1H); 8.11 (s, 1H); 8.40 (s, 1H); 13.95 (br s, 1H).	352.2

B17	 2-(1-isobutylpyrazol-4-yl)-5-propyl-3H-imidazo[2,1-b]purin-4-one	DMSO-d ₆ : δ 0.87 (d, J = 6.4 Hz, 6H); 0.91 (t, J = 7.6 Hz, 3H); 1.69-1.75 (m, 2H); 2.10-2.17 (m, 1H); 3.97 (d, J = 6.8 Hz, 2H); 4.14 (t, J = 8.0 Hz, 2H); 7.08 (br s, 1H); 7.57 (br s, 1H); 7.96 (br s, 1H); 8.19 (br s, 1H).	340.2
B18	 2-[1-(cyclopropylmethyl)pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one	DMSO-d ₆ : δ 0.39-0.43 (m, 2H); 0.55-0.60 (m, 2H); 0.92 (t, J = 7.6 Hz, 3H); 1.26-1.30 (m, 1H); 1.72-1.78 (m, 2H); 4.05 (d, J = 7.6 Hz, 2H); 4.18 (t, J = 7.2 Hz, 2H); 7.17 (d, J = 1.6 Hz, 1H); 7.69 (d, J = 1.6 Hz, 1H); 8.12 (s, 1H); 8.48 (s, 1H); 13.80 (br s, 1H).	338.2
B19	 2-[1-(2,2-dimethylpropyl)pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one	DMSO-d ₆ : δ 0.91-0.94 (m, 12H); 1.72-1.78 (m, 2H); 4.00 (s, 2H); 4.17 (t, J = 7.2 Hz, 2H); 7.25 (br s, 1H); 7.74 (br s, 1H); 8.12 (s, 1H); 8.37 (s, 1H); 13.95 (br s, 1H).	354.3
B20	 5-propyl-2-(1-sec-butylpyrazol-4-yl)-3H-imidazo[2,1-b]purin-4-one	DMSO-d ₆ : δ 0.74 (t, J = 7.2 Hz, 3H); 0.92 (t, J = 7.2 Hz, 3H); 1.45 (d, J = 6.4 Hz, 3H); 1.72-1.86 (m, 4H); 4.18 (d, J = 7.6 Hz, 2H); 4.33-4.38 (m, 1H); 7.17 (d, J = 1.6 Hz, 1H); 7.67 (d, J = 1.2 Hz, 1H); 8.14 (s, 1H); 8.44 (s, 1H); 13.90 (br s, 1H).	340.2

B21	 5-propyl-2-[1-(tetrahydrofuran-2-ylmethyl)pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one	DMSO-d₆: δ 0.92 (t, J = 7.2 Hz, 3H); 1.60-1.63 (m, 1H); 1.72-1.81 (m, 4H); 1.93-1.96 (m, 1H); 3.63-3.68 (m, 1H); 3.74-3.79 (m, 1H); 4.16-4.28 (m, 5H); 7.17 (d, J = 2.0 Hz, 1H); 7.69 (d, J = 1.6 Hz, 1H); 8.11 (s, 1H); 8.39 (s, 1H); 13.15 (br s, 1H).	368.2
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Example C1: 2-[1-[[5-oxo-1-[2-(trifluoromethyl)-4-pyridyl]pyrrolidin-3-yl]methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one



Step 1: 2-[1-[[5-oxo-1-[6-(trifluoromethyl)-3-pyridyl]pyrrolidin-3-yl]methyl]pyrazol-4-yl]-5-propyl-3-(2-trimethylsilylethoxymethyl)imidazo[2,1-b]purin-4-one (3.2)

Synthesis of 5-oxo-1-[2-(trifluoromethyl)-4-pyridyl]pyrrolidine-3-carboxylic acid

A mixture of 2-(trifluoromethyl)pyridin-5-amine (1.12 g, 6.92 mmol) and itaconic acid (1.0g, 7.69 mmol) was heated at 130-135 °C for 10 hours. Reaction completion was confirmed by TLC then cooled to room temperature, diluted with diethyl ether, solid was filtered off, dried to obtain 5-oxo-1-[6-(trifluoromethyl)-3-pyridyl]pyrrolidine-3-carboxylic acid as a off white solid (0.49 g, 23%).

MS(ESI)m/z: 275.1 (M + 1); ¹H NMR : Not recorded

Synthesis of ethyl 5-oxo-1-[2-(trifluoromethyl)-4-pyridyl]pyrrolidine-3-carboxylate

A mixture of 5-oxo-1-[6-(trifluoromethyl)-3-pyridyl]pyrrolidine-3-carboxylic acid (0.4 g, 2.42 mmol), sulfuric acid (0.5 mL), and ethanol (20 mL) was heated at 80-85 °C for 10 hours. Reaction completion was confirmed by TLC and cooled to room temperature. The organic volatiles were evaporated under vacuo to obtain a crude product. The residue dissolved in ethyl acetate (20 mL) and washed with NaHCO₃ solution (2 x 20 mL). Organic layer was washed with brine, dried over Na₂SO₄ and evaporated under vacuo to obtain ethyl 5-oxo-1-[6-(trifluoromethyl)-3-pyridyl]pyrrolidine-3-carboxylate as yellow oil (0.43 g, 98 %).

MS(ESI)m/z: 303.1 (M + 1); ¹H NMR : Not recorded

Synthesis of 4-(hydroxymethyl)-1-[6-(trifluoromethyl)-3-pyridyl]pyrrolidin-2-one

A mixture of ethyl 5-oxo-1-[6-(trifluoromethyl)-3-pyridyl]pyrrolidine-3-carboxylate (0.41 g, 1.37 mmol) and methanol (20 mL) were cooled to 10-15 °C and sodium borohydride (0.10 g, 2.74 mmol) was added portion wise over a period of 5 min and the reaction mixture was stirred for 9 hours at room temperature. Reaction completion was confirmed by TLC and concentrated under vacuo to obtain a crude product. To the residue water (20 mL), was added and aqueous solution was extracted with ethyl acetate (3x20 ml). Combined organic layer was washed with brine, dried over Na₂SO₄ and evaporated to afford crude which was purified by combiflash column chromatography using 40-50 % ethyl acetate in hexane as a mobile phase to obtain 4-(hydroxymethyl)-1-[6-(trifluoromethyl)-3-pyridyl]pyrrolidin-2-one as colorless oil (0.31 g, 88 %).

MS(ESI)m/z: 261.0 (M + 1); ¹H NMR (400 MHz, DMSO-*d*₆): δ 2.31-2.37 (m, 1H); 2.47-2.68 (m, 1H); 3.14-3.17 (m, 1H); 3.41-3.45 (m, 2H); 3.69-3.73 (m, 1H); 3.98-4.01 (m, 1H); 4.85-4.87 (m, 1H); 8.55 (br s, 1H); 8.70 (s, 1H); 9.06 (d, *J* = 2.0 Hz, 1H)

Synthesis of [5-oxo-1-[6-(trifluoromethyl)-3-pyridyl]pyrrolidin-3-yl]methyl methanesulfonate (3.1)

A mixture of 4-(hydroxymethyl)-1-[6-(trifluoromethyl)-3-pyridyl]pyrrolidin-2-one (0.25 g, 0.96 mmol), dichloromethane (7 mL) and triethyl amine (0.27 mL, 1.92 mmol) was cooled to 0 °C. To this solution methanesulfonyl chloride (0.089 mL, 1.15 mmol) was added over a period of 5 min and the reaction mixture was stirred for 2 hours at room temperature. Reaction completion was confirmed by TLC, added aqueous NaHCO₃ solution, and extracted by DCM (2x20 mL). Organic layer was washed with brine, dried over Na₂SO₄ and evaporated to obtain [5-oxo-1-[6-(trifluoromethyl)-3-pyridyl]pyrrolidin-3-yl]methyl methanesulfonate as yellow oil (0.30 g, 92 %).

MS(ESI)m/z:(M+1)339.1; ¹HNMR (400 MHz, DMSO-*d*₆): δ 2.43-2.47 (m, 1H); 2.74-2.82 (m, 1H); 2.93-2.96 (m, 1H); 3.32 (s, 3H); 3.74-3.78 (m, 1H); 4.07-4.12 (m, 1H); 4.28-4.34 (m, 2H); 7.93 (d, *J* = 8.8 Hz, 1H); 8.6-8.39 (m, 1H); 9.04 (d, *J* = 2.4 Hz, 1H)

Synthesis of 2-[1-[[5-oxo-1-[6-(trifluoromethyl)-3-pyridyl]pyrrolidin-3-yl]methyl]pyrazol-4-yl]-5-propyl-3-(2-trimethylsilylethoxymethyl)imidazo[2,1-b]purin-4-one

To a solution **2.2** (0.25 g, 0.605 mmol) in DMF (7 mL) was added cesium carbonate (0.394 g, 1.21 mmol), **3.1** (0.244 g, 0.726 mmol). The mixture was stirred at 80 °C for 16 hours. Reaction completion was confirmed by TLC then cooled to room temperature and added water, solid obtained was filtered, washed with cold water then washed with n-hexane, dried to afford the title compound **3.2** as off white solid (0.1 g, 25%).

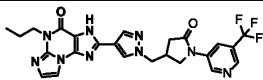
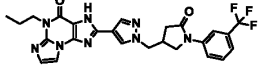
MS(ESI)m/z: 656.0 (M + 1); ¹H NMR : Not recorded

Step 2: Synthesis of 2-[1-[[5-oxo-1-[2-(trifluoromethyl)-4-pyridyl]pyrrolidin-3-yl]methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one

A solution of **3.2** (0.1 g, 0.15 mmol) in DCM (9 mL) was added TFA (1 mL) and stirred at room temperature for 4 hours. Reaction completion was confirmed by TLC then concentrated under vacuo to obtain a crude product. The residue was basified by aqueous NaHCO₃ solution up to pH (7-8) then solid obtained was filtered, washed with n-hexane, dried and purified by LCMS purification method to obtain the title compound **C1** as a white solid (0.070 g, 87 %).

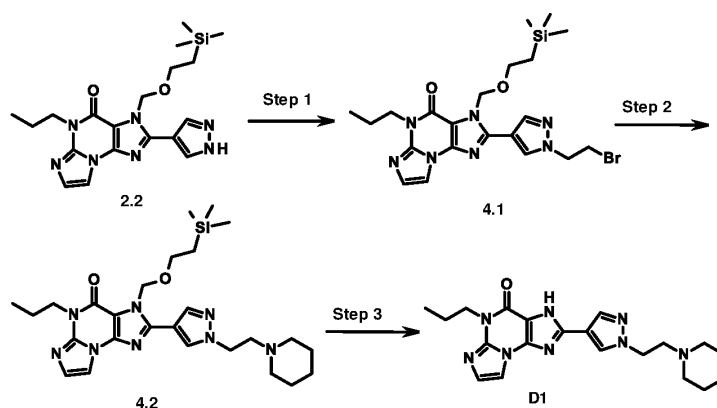
- MS(ESI)m/z: 526.2 (M + 1); ¹H NMR (400 MHz, DMSO-d₆): δ 0.92 (t, *J* = 7.2 Hz, 3H); 1.71-1.78 (m, 2H); 2.51-2.53 (m, 1H); 2.72-2.79 (m, 1H); 3.08-3.09 (m, 1H); 3.77-3.82 (m, 1H); 4.04-4.08 (m, 1H); 4.19 (t, *J* = 7.2 Hz, 2H); 4.38 (d, *J* = 7.2 Hz, 2H); 7.16 (d, *J* = 1.6 Hz, 1H); 7.65 (d, *J* = 1.6 Hz, 1H); 7.89 (d, *J* = 8.4 Hz, 1H);
- 5 8.14 (s, 1H); 8.27-8.30 (m, 1H); 8.48 (s, 1H); 9.01 (d, *J* = 2.4 Hz, 1H); 13.9 (br s, 1H)

Following examples as shown in Table were prepared according to similar sequence of procedures as used for the synthesis of **Example C1**

Ex. No.	Structure IUPAC Name	¹ H NMR (400 MHz) data	MS(ESI)m/z: (M+1)
C2	 2-[1-[[5-oxo-1-[5-(trifluoromethyl)-3-pyridyl]pyrrolidin-3-yl]methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one	DMSO-d ₆ : δ 0.92 (t, <i>J</i> = 7.6 Hz, 3H); 1.72-1.78 (m, 2H); 2.51-2.53 (m, 1H); 2.75-2.79 (m, 1H); 3.07-3.09 (m, 1H); 3.79-3.82 (m, 1H); 4.07-4.09 (m, 1H); 4.19 (t, <i>J</i> = 7.2 Hz, 2H); 4.38 (d, <i>J</i> = 8.8 Hz, 2H); 7.16 (s, 1H); 7.65 (s, 1H); 8.15 (s, 1H); 8.49 (br s, 2H); 8.71 (s, 1H); 9.03 (s, 1H); 13.9 (br s, 1H).	526.2
C3	 2-[1-[[5-oxo-1-[3-(trifluoromethyl)phenyl]pyrrolidin-3-yl]methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one	DMSO-d ₆ : δ 0.90 (t, <i>J</i> = 7.2 Hz, 3H); 1.70-1.76 (m, 2H); 2.63-2.74 (m, 2H); 3.00-3.15 (m, 1H); 3.71-3.75 (m, 1H); 4.00 (t, <i>J</i> = 8.0 Hz, 1H); 4.16 (t, <i>J</i> = 6.8 Hz, 2H); 4.36 (d, <i>J</i> = 6.8 Hz, 2H); 7.15 (dd, <i>J</i> = 1.6 Hz, 1H); 7.45 (d, <i>J</i> = 8.0 Hz, 1H); 7.59 (dd, <i>J</i> = 8.0 Hz, 1H); 7.65 (dd, <i>J</i> = 1.6 Hz, 1H); 7.74 (d, <i>J</i> = 8.4 Hz, 1H); 8.15 (s, 1H); 8.49 (br s, 2H); 8.71 (s, 1H); 9.03 (s, 1H); 13.9 (br s, 1H).	525.2

	yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one	1H); 8.11-8.15 (m, 2H); 8.49 (s, 1H); 13.88 (br s, 1H).	
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Example D1: 2-[1-[2-(1-piperidyl)ethyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one



5 Step 1: Synthesis of 2-[1-(2-bromoethyl)pyrazol-4-yl]-5-propyl-3-(2-trimethylsilylethoxymethyl)imidazo[2,1-b]purin-4-one

The title compound **4.1** was obtained as an off-white solid (0.35 g, 69 %) in a similar manner to that of **example B1 step 4** using the compound **2.2** (0.4 g, 0.97 mmol), potassium carbonate (0.4 g, 2.90 mmol) and 1,2-dibromoethane (0.33 mL, 3.87 mmol).

MS(ESI)m/z: 519.9, 522.9 (M + 1); ¹H NMR (400 MHz, DMSO-d₆): δ -0.086 (s, 9H); 0.86-0.92 (m, 5H); 1.72-1.76 (m, 2H); 3.70 (t, J = 8.0 Hz, 2H); 3.92 (t, J = 5.6 Hz, 2H); 4.18 (t, J = 7.2 Hz, 2H); 4.64 (t, J = 5.6 Hz, 2H); 5.92 (s, 2H); 7.19 (d, J = 1.6 Hz, 1H); 7.72 (d, J = 1.2 Hz, 1H); 8.10 (s, 1H); 8.48 (s, 1H)

15 Step 2: Synthesis of 2-[1-[2-(1-piperidyl)ethyl]pyrazol-4-yl]-5-propyl-3-(2-trimethylsilylethoxymethyl)imidazo[2,1-b]purin-4-one

To a solution **4.1** (0.15 g, 0.29 mmol) in DMF (5 mL) was added DIPEA (0.14 mL, 0.86 mmol), and piperidine (0.085 mL, 0.86 mmol). The mixture was stirred at 60 °C for 16 hours. Reaction completion was confirmed by TLC then cooled to room

temperature and added water (50 mL). Aqueous layer was extracted with ethyl acetate (3x20 mL), washed with brine (20 mL), dried over Na₂SO₄ and concentrated under vacuo to obtain a crude product. The residue was purified by LCMS purification method to obtain the title compound **4.2** as white solid. (0.05 g, 33%).

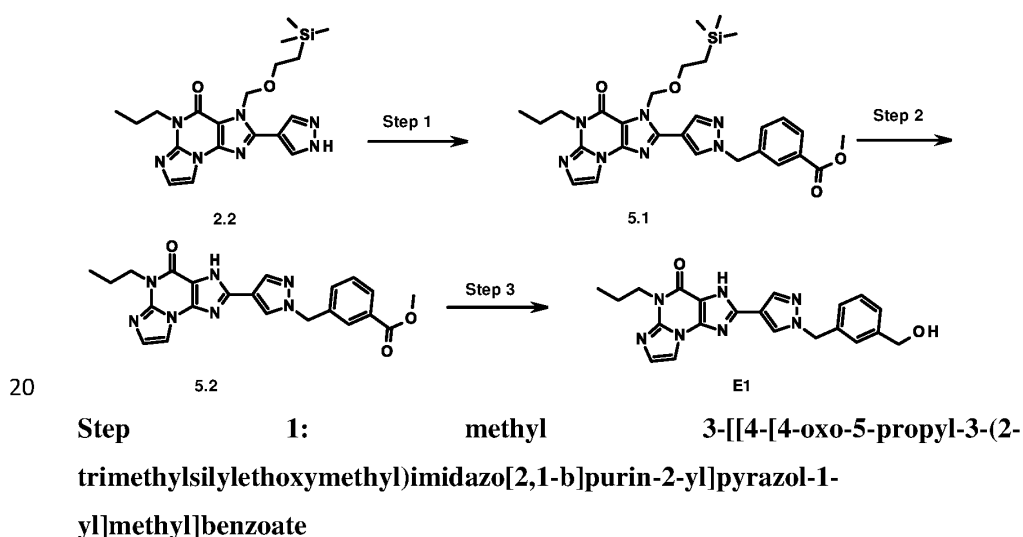
- 5 MS(ESI)m/z: 525.4 (M + 1); ¹H NMR (400 MHz, DMSO-d₆): δ -0.088 (s, 9H); 0.86-0.93 (m, 9H); 1.23-1.28 (m, 4H); 1.74-1.82 (m, 4H); 2.49-2.50 (m, 2H); 3.71 (t, *J* = 7.2 Hz, 2H); 4.17-4.24 (m, 4H); 5.94 (s, 2H); 7.19 (d, *J* = 1.6 Hz, 1H); 7.72 (d, *J* = 1.6 Hz, 1H); 8.05 (s, 1H); 8.41 (s, 1H)

10 **Step 3: Synthesis of 2-[1-[2-(1-piperidyl)ethyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one**

The title compound **D1** was obtained as an off-white solid (0.02 g., 54 %) in a similar manner to that of **Example B1 step 5** using the compound **4.2** (0.05 g, 0.095 mmol) and ethanol:2N HCl (10 mL)

- 15 MS(ESI)m/z: 395.3 (M + 1); ¹H NMR (400 MHz, DMSO-d₆): δ 0.93 (t, *J* = 7.6 Hz, 3H); 1.63-1.72 (m, 3H); 1.74-1.1.84 (m, 4H); 2.93-2.96 (m, 3H); 3.45-3.48 (m, 2H); 3.60 (q, *J* = 6.0 Hz, 2H); 4.18 (t, *J* = 7.2 Hz, 2H); 4.65 (t, *J* = 5.6 Hz, 2H); 7.18 (d, *J* = 1.2 Hz, 1H); 7.66 (d, *J* = 1.2 Hz, 1H); 8.24 (s, 1H); 8.54 (s, 1H); 13.95 (br s, 1H)

Example E1: 2-[1-[3-(hydroxymethyl)phenyl]methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one



The title compound **5.1** was obtained as an off-white solid (0.4 g, 98 %) in a similar manner to that of **example B1 step 4** using the compound **2.2** (0.3 g, 0.72 mmol), potassium carbonate (0.15 g, 1.09 mmol) and methyl 3-(bromomethyl)benzoate (0.18 g, 0.799 mmol).

- 5 MS(ESI)m/z: 562.0 (M + 1); ¹H NMR (400 MHz, DMSO-d₆): δ -0.117 (s, 9H); 0.84-0.93 (m, 5H); 1.72-1.78 (m, 2H); 3.69 (t, *J* = 8.0 Hz, 2H); 3.85 (s, 3H); 4.19 (t, *J* = 6.8 Hz, 2H); 5.56 (s, 2H); 5.93 (s, 2H); 7.20 (d, *J* = 1.6 Hz, 1H); 7.54 (t, *J* = 7.6 Hz, 1H); 7.63 (d, *J* = 8.0 Hz, 1H); 7.73 (d, *J* = 1.6 Hz, 1H); 7.92 (dd, *J* = 1.6, 9.2 Hz, 1H); 7.96 (d, *J* = 16 Hz, 1H); 8.10 (s, 1H); 8.59 (s, 1H).

10 **Step 2: methyl 3-[[4-(4-oxo-5-propyl-3H-imidazo[2,1-b]purin-2-yl)pyrazol-1-yl]methyl]benzoate**

The title compound **5.2** was obtained as an off-white solid (0.3 g, 98 %) in a similar manner to that of **Example B1 step 5** using the compound **5.1** (0.4 g, 0.71 mmol) and ethanol:2N HCl (24 mL)

- 15 MS(ESI)m/z: 432.2 (M + 1); ¹H NMR (400 MHz, DMSO-d₆): δ 0.92 (t, *J* = 7.6 Hz, 3H); 1.72-1.77 (m, 2H); 3.31 (s, 3H); 4.15-4.19 (m, 2H); 5.52 (s, 2H); 7.17 (d, *J* = 1.6 Hz, 1H); 7.53-7.56 (m, 1H); 7.59-7.61 (m, 1H); 7.68 (d, *J* = 1.6 Hz, 1H); 7.90-7.93 (m, 2H); 8.17 (s, 1H); 8.55 (s, 1H); 13.86 (s, 1H).

20 **Step 3: 2-[1-[[3-(hydroxymethyl)phenyl]methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one**

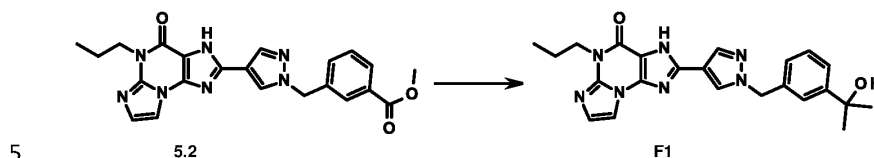
To a solution of **5.2** (0.05 g, 0.116 mmol) in DCM (10 mL) was added DIBAL (0.32 mL, 0.58 mmol, 25 % solution in Toluene) at -50 °C and the reaction mixture was warm up to 0 °C. Reaction completion was confirmed by TLC then reaction mixture was quenched with ammonium chloride solution and extracted with 5% MeOH in

25 DCM (3 x 20 mL). The combined organic layer was washed with brine and dried over Na₂SO₄ and concentrated under vacuo to obtain a crude product. The residue was purified by preparative TLC to obtain the title compound **E1** as off white solid (0.010 g, 21 %).

- 30 MS(ESI)m/z: 404.2 (M + 1); ¹H NMR (400 MHz, DMSO-d₆): δ 0.92 (t, *J* = 7.6 Hz, 3H); 1.72-1.78 (m, 2H); 4.17 (t, *J* = 7.6 Hz, 2H); 4.48 (d, *J* = 6.0 Hz, 2H); 5.21 (d, *J*

= 6.0 Hz, 1H); 5.40 (s, 2H); 7.16-7.20 (m, 2H); 7.24-7.34 (m, 3H); 7.68 (d, $J = 1.2$ Hz, 1H); 8.14 (s, 1H); 8.49 (s, 1H); 13.93 (br s, 1H).

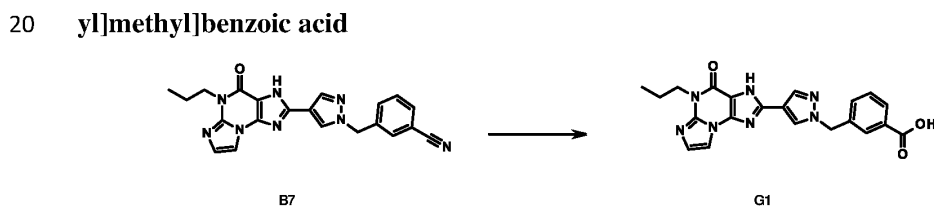
Example F1: 2-[1-[[3-(1-hydroxy-1-methyl-ethyl)phenyl]methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one



To a solution of **5.2** (0.05 g, 0.115 mmol) in THF (10 mL) was added methylmagnesium bromide (0.57 mL, 0.57 mmol, 1M solution in THF) at -50 °C and the reaction mixture was warm to 0 °C. Reaction completion was confirmed by TLC then reaction mixture was quenched with ammonium chloride solution and extracted with 5% MeOH in DCM (3 x 20 mL). The combined organic layer was washed with brine and dried over Na₂SO₄ and concentrated under vacuo to obtain a crude product. The residue was purified by preparative TLC to obtain the title compound **F1** as an off white solid (0.01 g, 20 %).

MS(ESI)m/z: 432.2 (M + 1); ¹H NMR (400 MHz, DMSO-d₆): δ 0.92 (t, $J = 7.6$ Hz, 3H); 1.40 (s, 6H); 1.71-1.77 (m, 2H); 4.17 (t, $J = 8.0$ Hz, 2H); 5.02 (s, 1H); 5.40(s, 2H); 7.11 (d, $J = 8.0$ Hz, 1H); 7.16 (d, $J = 1.6$ Hz, 1H); 7.29 (t, $J = 8.0$ Hz, 1H); 7.39 (d, $J = 8.0$ Hz, 1H); 7.49 (s, 1H); 7.68 (d, $J = 1.6$ Hz, 1H); 8.15 (s, 1H); 8.49 (s, 1H); 13.86 (br s, 1H).

Example G1: 3-[[4-(4-oxo-5-propyl-3H-imidazo[2,1-b]purin-2-yl)pyrazol-1-yl]methyl]benzoic acid

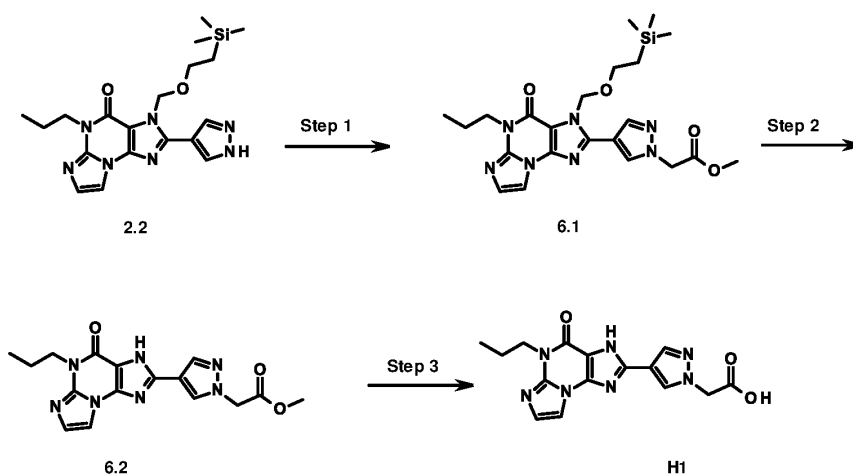


To a solution of **B7** (0.07 g, 0.175 mmol) in methanol:water (3:1, 10 mL) was added NaOH (0.021 g, 0.527 mmol) and the reaction mixture was stirred at 80 °C for 16 hours. Reaction completion was confirmed by TLC then reaction mixture was cooled

to room temperature and evaporated to dryness. Acidified with 2N HCl to pH (3-4) and solid obtained was filtered, washed with n-hexane and dried to obtain the title compound **G1** as off white solid (0.02 g, 27 %).

MS(ESI)m/z: 418.0 (M + 1); ¹H NMR (400 MHz, DMSO-d₆): δ 0.92 (t, *J* = 7.2 Hz, 3H); 1.72-1.77 (m, 2H); 4.17 (t, *J* = 7.6 Hz, 2H); 5.47 (s, 2H); 7.16 (d, *J* = 1.6 Hz, 1H); 7.39 (br s, 1H); 7.45-7.47 (m, 2H); 7.68 (d, *J* = 1.6 Hz, 1H); 7.81-7.84 (m, 1H); 7.99 (br s, 1H); 8.16 (s, 1H); 8.53 (s, 1H); 13.92 (br s, 1H)

Example H1: 2-[4-(4-oxo-5-propyl-3H-imidazo[2,1-b]purin-2-yl)pyrazol-1-yl]acetic acid



Step 1: methyl 2-[4-[4-oxo-5-propyl-3-(2-trimethylsilylethoxymethyl)imidazo[2,1-b]purin-2-yl]pyrazol-1-yl]acetate

The title compound **6.1** was obtained as an off-white solid (0.2 g, 83 %) in a similar manner to that of **example B1 step 4** using the compound **2.2** (0.2 g, 0.484 mmol), potassium carbonate (0.14 g, 1.06 mmol) and methyl bromoacetate (0.06 g, 0.58 mmol).

MS(ESI)m/z: 486.0 (M + 1); ¹H NMR (400 MHz, DMSO-d₆): δ -0.11 (s, 9H); 0.96-1.01 (m, 5H); 1.81-1.86 (m, 2H); 3.78-3.82 (m, 5H); 4.28 (t, *J* = 6.8 Hz, 2H); 5.33 (s, 2H); 6.01 (s, 2H); 7.28 (d, *J* = 1.6 Hz, 1H); 7.82 (d, *J* = 1.6 Hz, 1H); 8.17 (s, 1H); 8.54 (s, 1H)

Step 2: methyl 2-[4-(4-oxo-5-propyl-3H-imidazo[2,1-b]purin-2-yl)pyrazol-1-yl]acetate

The title compound **6.2** was obtained as an off-white solid (0.13 g, 88 %) in a similar manner to that of **Example B1 step 5** using the compound **6.1** (0.2 g, 0.4 mmol) and ethanol:2N HCl (12 mL)

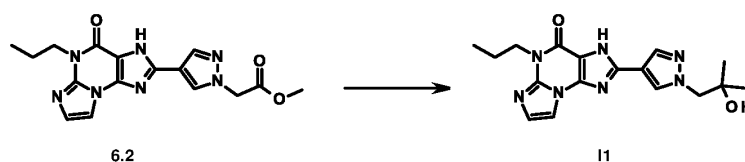
MS(ESI)m/z: 356.0 (M + 1); ¹H NMR (400 MHz, DMSO-d₆): Not recorded

Step 3: 2-[4-(4-oxo-5-propyl-3H-imidazo[2,1-b]purin-2-yl)pyrazol-1-yl]acetic acid

To a solution of **6.2** (0.2 g, 0.54 mmol) in ethanol:water (2:1) (10 mL) was added NaOH (0.065 g, 1.62 mmol) and the reaction mixture was stirred at 80 °C for 3 hours. Reaction completion was confirmed by TLC then reaction mixture was cooled to room temperature and evaporated to dryness. The residue was acidified with 2N HCl to pH 3 and solid obtained was filtered, washed n-hexane dried to obtain the title compound **H1** as an off white solid (0.17 g, 92 %).

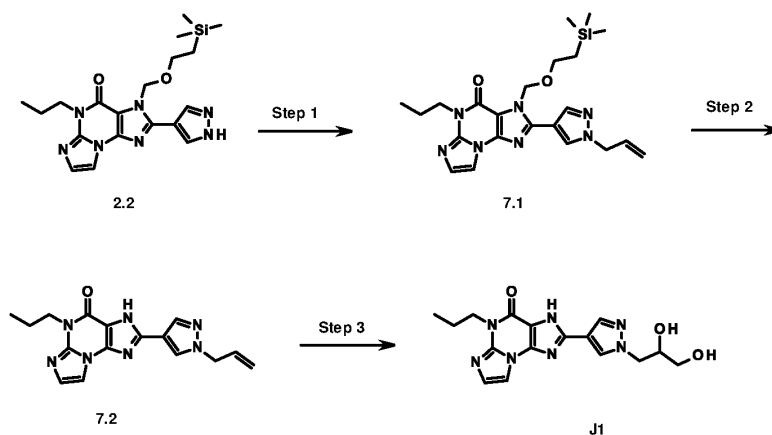
MS(ESI)m/z: 342.2 (M + 1); ¹H NMR (400 MHz, DMSO-d₆): δ 0.93 (t, *J* = 7.6 Hz, 3H); 1.75 (q, *J* = 7.2 Hz, 2H); 4.18 (t, *J* = 7.6 Hz, 2H); 5.08 (s, 2H); 7.18 (br s, 1H); 7.77 (br s, 1H); 8.14 (s, 1H); 8.43 (s, 1H); 13.22 (br s, 1H); 13.93 (br s, 1H)

Example I1: 2-[1-(2-hydroxy-2-methyl-propyl)pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one



The title compound **I1** was obtained as an off-white solid (0.01 g, 21 %) in a similar manner to that of **example F1** using the compound **6.2** (0.05 g, 0.14 mmol), THF (10 mL) and methylmagnesium bromide (0.57 mL, 0.57 mmol, 1M solution in THF) MS(ESI)m/z: 356.2 (M + 1); ¹H NMR (400 MHz, DMSO-d₆): δ 0.92 (t, *J* = 7.6 Hz, 3H); 1.09 (s, 6H); 1.72-1.78 (m, 2H); 4.09 (s, 2H); 4.19 (t, *J* = 7.6 Hz, 2H); 4.78 (s, 1H); 7.16 (s, 1H); 7.71 (s, 1H); 8.10 (s, 1H); 8.37 (s, 1H); 13.86 (br s, 1H).

Example J1: 2-[1-(2,3-dihydroxypropyl)pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one



Step 1: 2-(1-allylpyrazol-4-yl)-5-propyl-3-(2-trimethylsilylethoxymethyl)imidazo[2,1-b]purin-4-one

The title compound **7.1** was obtained as an off-white solid (0.15 g, 91 %) in a similar manner to that of **example B1 step 4** using the compound **2.2** (0.15 g, 0.36 mmol), potassium carbonate (0.12 g, 0.90 mmol) and allyl bromide (0.044 g, 0.36 mmol).
 MS(ESI)m/z: 454.0 (M + 1); ¹H NMR (400 MHz, DMSO-d₆): δ -0.11 (s, 9H); 0.92-1.01 (m, 5H); 1.79-1.86 (m, 2H); 3.80 (t, *J* = 8.0 Hz, 2H); 4.28 (t, *J* = 6.8 Hz, 2H); 4.98 (d, *J* = 5.2 Hz, 2H); 5.27-5.36 (m, 2H); 6.02 (s, 2H); 6.11-6.19 (m, 1H); 7.28 (s, 1H); 7.82 (s, 1H); 8.17 (s, 1H); 8.48 (s, 1H).

Step 2: 2-(1-allylpyrazol-4-yl)-5-propyl-3H-imidazo[2,1-b]purin-4-one

The title compound **7.2** was obtained as an off-white solid (0.088 g, 83 %) in a similar manner to that of **Example B1 step 5** using the compound **7.1** (0.15 g, 0.33 mmol).
 MS(ESI)m/z: 324.0 (M + 1); ¹H NMR (400 MHz, DMSO-d₆): δ 0.94 (t, *J* = 7.6 Hz, 3H); 1.72-1.75 (m, 2H); 4.17 (t, *J* = 7.2 Hz, 2H); 4.86 (d, *J* = 6.0 Hz, 2H); 5.18-5.27 (m, 2H); 6.01-6.09 (m, 1H); 7.38 (s, 1H); 7.84 (s, 1H); 8.15 (s, 1H); 8.42 (s, 1H); 14.12 (br s, 1H).

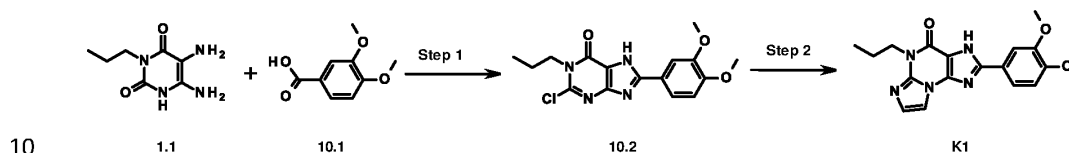
Step 3: 2-[1-(2,3-dihydroxypropyl)pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one

Osmium tetroxide (0.005 g, 0.019 mmol) and *N*-methylmorpholine *N*-oxide (0.047 g, 0.40 mmol) was added to the suspended mixture of **7.2** (0.088 g, 0.27 mmol) in acetone-water (1:1, 10 mL) at room temperature and the reaction mixture was stirred

for overnight. Reaction completion was confirmed by TLC. The solid obtained was filtered and purified using preparative TLC method to obtain the title compound **J1** as an off white solid (0.018 g, 33 %).

MS(ESI)m/z: 358.2 (M + 1); ¹HNMR (400 MHz, DMSO-*d*₆): 0.93 (t, *J* = 7.6 Hz, 3H); 1.73-1.79(m, 2H); 3.32-3.40 (m, 2H); 3.80-3.82 (m, 1H); 4.04-4.09 (m, 1H); 4.18 (t, *J* = 7.2 Hz, 2H); 4.28-4.32 (m, 1H); 4.79 (t, *J* = 6.0 Hz, 1H); 5.07 (d, *J* = 5.2 Hz, 1H); 7.17 (d, *J* = 1.6 Hz, 1H); 7.71 (d, *J* = 1.6 Hz, 1H); 8.11 (s, 1H); 8.37 (s, 1H); 13.86 (s, 1H)

Example K1: 2-(3,4-dimethoxyphenyl)-5-propyl-3H-imidazo[2,1-b]purin-4-one



Step 1: 2-chloro-8-(3,4-dimethoxyphenyl)-1-propyl-7H-purin-6-one

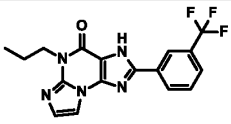
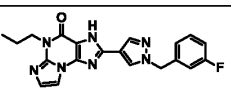
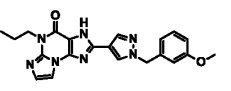
A mixture of **1.1** (1.0 g, 5.43 mmol), **10.1** (0.99 g, 5.43 mmol) and POCl₃ (10 mL) were heated at 120-125 °C for 72 hours. Reaction completion was confirmed by TLC, mixture was cooled to 20-25 °C. It was then concentrated under vacuuo and to the residue cold water was added slowly and solid material was separated. It was filtered off and washed with cold water, dried under vacuuo. The crude product was purified by column chromatography using silica gel (230-400 mesh) and 0.5 to 4 % methanol in DCM as an eluent to obtain **10.2** as a pale yellow solid. (1.1 g, 58 %)

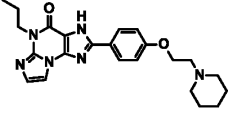
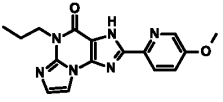
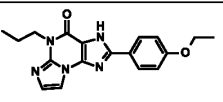
ESI-MS(m/z): 349.2 (M + 1); ¹HNMR Not recorded

Step 2: 2-(3,4-dimethoxyphenyl)-5-propyl-3H-imidazo[2,1-b]purin-4-one The title compound was obtained as an yellow solid (0.11 g, 20 %) in a similar manner to that of **Example A1 step 4** using the compound **8.2** (0.2 g, 0.575 mmol), NMP (5 mL), DIPEA (0.38 mL, 2.30 mmol), and aminoacetaldehyde dimethyl acetal (0.25 mL, 2.29 mmol).

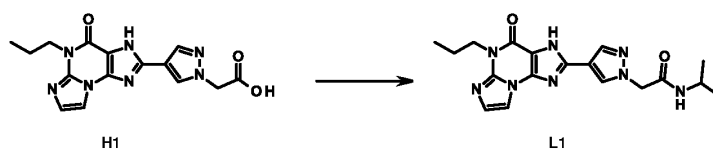
MS(ESI)m/z: 354.2 (M + 1); ¹HNMR (400 MHz, DMSO-*d*₆): δ 0.91 (t, *J* = 7.2 Hz, 3H); 1.73-1.75 (m, 2H); 3.79 (s, 3H); 3.85 (s, 3H); 4.17 (t, *J* = 7.2 Hz, 2H); 7.08 (d, *J* = 8.4 Hz, 1H); 7.14 (s, 1H); 7.72-7.78 (m, 3H); 13.96 (br s, 1H).

Following examples as shown in Table were prepared according to similar sequence of procedures as used for the synthesis of **Example K1**

Ex. No.	Structure IUPAC Name	¹ H NMR(400 MHz) data	MS(ESI)m/z: (M+1)
K2	 5-propyl-2-[3-(trifluoromethyl)phenyl]-3H-imidazo[2,1-b]purin-4-one	DMSO-d ₆ : δ 0.94 (t, <i>J</i> = 7.2 Hz, 3H); 1.77 (q, <i>J</i> = 7.2 Hz, 2H); 4.20 (t, <i>J</i> = 7.6 Hz, 2H); 7.19 (d, <i>J</i> = 1.2 Hz, 1H); 7.78-7.82 (m, 2H); 7.88 (d, <i>J</i> = 8.0 Hz, 1H); 8.49 (d, <i>J</i> = 8.0 Hz, 1H); 8.59 (s, 1H); 14.49 (br s, 1H)	362.1
K3	 2-[1-[(3-fluorophenyl)methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one	DMSO-d ₆ : δ 0.92 (t, <i>J</i> = 8.0 Hz, 3H); 1.75 (d, <i>J</i> = 7.2 Hz, 2H); 4.17 (t, <i>J</i> = 7.6 Hz, 2H); 5.45 (s, 2H); 7.14-7.19 (m, 4H); 7.40-7.44 (m, 1H); 7.68 (d, <i>J</i> = 1.6 Hz, 1H); 8.17 (s, 1H); 8.53 (s, 1H); 13.89 (br s, 1H).	392.2
K4	 2-[1-[(3-methoxyphenyl)methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one	DMSO-d ₆ : δ 0.92 (t, <i>J</i> = 7.6 Hz, 3H); 1.72-1.78 (m, 2H); 3.74 (s, 3H); 4.17 (t, <i>J</i> = 7.2 Hz, 2H); 5.38 (s, 2H); 6.86-6.90 (m, 3H); 7.16 (d, <i>J</i> = 1.6 Hz, 1H); 7.27-7.31 (m, 1H); 7.68 (d, <i>J</i> = 2 Hz, 1H); 8.15 (s, 1H); 8.49 (s, 1H); 13.87 (br s, 1H).	404.2

	imidazo[2,1-b]purin-4-one		
K5	 2-[4-[2-(1-piperidyl)ethoxy]phenyl]-5-propyl-3H-imidazo[2,1-b]purin-4-one	DMSO-d ₆ : δ 0.92 (t, <i>J</i> = 7.6 Hz, 3H); 1.38-1.39 (m, 2H); 1.48-1.53 (m, 4H); 1.73-1.79 (m, 2H); 2.45 (br s, 4H); 2.69 (t, <i>J</i> = 6.0 Hz, 2H); 4.13-4.20 (m, 4H); 7.09 (d, <i>J</i> = 8.8 Hz, 2H); 7.17 (d, <i>J</i> = 0.8 Hz, 1H); 7.74 (d, <i>J</i> = 1.2 Hz, 1H); 8.14 (d, <i>J</i> = 8.8 Hz, 2H); 13.58 (br s, 1H)	421.3
K6	 2-(5-methoxy-2-pyridyl)-5-propyl-3H-imidazo[2,1-b]purin-4-one	DMSO-d ₆ : δ 0.92 (t, <i>J</i> = 8.0 Hz, 3H); 1.75-1.75 (m, 2H); 3.75 (s, 3H); 4.11-4.19 (m, 2H); 7.16 (br s, 1H); 7.72 (br s, 1H); 7.78 (d, <i>J</i> = 8.8 Hz, 1H); 7.99 (br s, 1H); 8.20 (d, <i>J</i> = 8.4 Hz, 1H)	325.2
K7	 2-(4-ethoxyphenyl)-5-propyl-3H-imidazo[2,1-b]purin-4-one	DMSO-d ₆ : δ 0.93 (t, <i>J</i> = 7.2 Hz, 3H); 1.36 (t, <i>J</i> = 6.8 Hz, 3H); 1.74-1.80 (m, 2H); 4.09-4.14 (m, 2H); 4.19 (t, <i>J</i> = 7.6 Hz, 2H); 7.08 (d, <i>J</i> = 8.4 Hz, 2H); 7.18 (br s, 1H); 7.74 (br s, 1H); 8.14 (d, <i>J</i> = 8.4 Hz, 2H); 13.95 (br s, 1H)	338.2

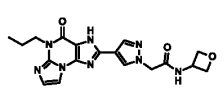
Example L1: N-isopropyl-2-[4-(4-oxo-5-propyl-3H-imidazo[2,1-b]purin-2-yl)pyrazol-1-yl]acetamide



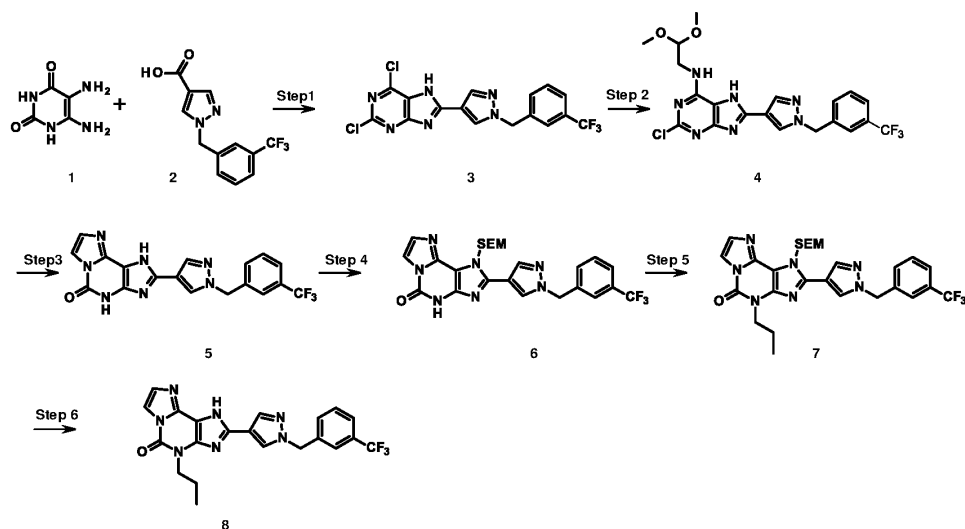
To a solution **H1** (0.05 g, 0.14 mmol) in DMF (2 mL) was added DIPEA (0.071 mL, 0.42 mmol), isopropyl amine (0.013 mL, 0.15 mmol), EDCI.HCl (0.04 g, 0.21 mmol) and hydroxyl benzotriazole (0.028 g, 0.21 mmol). The mixture was stirred at 25 °C for 16 hours. Reaction completion was confirmed by TLC and added water (20 mL). Solid material precipitated was filtered off and washed with cold water, dried under vacuuo. The crude product was purified by combiflash column chromatography to obtain the title compound **O1** as off white solid. (0.015 g, 27%).

MS(ESI)m/z: 383.2 (M + 1); ¹H NMR (400 MHz, DMSO-d₆): δ 0.92 (t, *J* = 7.6 Hz, 3H); 1.09 (d, *J* = 6.8 Hz, 6H); 1.72-1.78 (m, 2H); 3.84-3.86 (m, 1H); 4.18 (t, *J* = 8.0 Hz, 2H); 4.84 (s, 2H); 7.17 (br s, 1H); 7.70 (br s, 1H); 8.11 (s, 1H); 8.15 (d, *J* = 6.8 Hz, 1H); 8.39 (s, 1H); 13.50 (br s, 1H)

Following examples as shown in Table were prepared according to similar sequence of procedures as used for the synthesis of **Example L1**

Ex. No.	Structure IUPAC Name	¹ H NMR(400 MHz) data	MS(ESI)m/z: (M+1)
L2	 N-(oxetan-3-yl)-2-[4-(4-oxo-5-propyl-3H-imidazo[2,1-b]purin-2-yl)pyrazol-1-yl]acetamide	DMSO-d ₆ :δ 0.92 (t, <i>J</i> = 7.2 Hz, 3H); 1.72-1.78 (m, 2H); 4.18 (t, <i>J</i> = 7.2 Hz, 2H); 4.45 (t, <i>J</i> = 6.4 Hz, 2H); 4.73 (t, <i>J</i> = 6.4 Hz, 2H); 4.79-4.83 (m, 1H); 4.92 (s, 2H); 7.17 (d, <i>J</i> = 1.6 Hz, 1H); 7.70 (d, <i>J</i> = 1.6 Hz, 1H); 8.11 (s, 1H); 8.40 (s, 1H); 9.04 (d, <i>J</i> = 6.8 Hz, 1H); 13.50 (br s, 1H)	397.2

Example: 4-propyl-2-[1-[[3-(trifluoromethyl)phenyl]methyl] pyrazol-4-yl]-1H-imidazo[2,1-f]purin-5-one



Step 1: 2,6-dichloro-8-[1-[[3-(trifluoromethyl)phenyl]methyl]pyrazol-4-yl]-7H-purine

- 5 A mixture of **1** (3.94 g, 27.80 mmol), **2** (5 g, 18.52 mmol) and POCl₃ (50 mL) were heated at 120-125 °C for 72 hours. Reaction completion was confirmed by TLC, mixture was cooled to 20-25 °C. It was then concentrated under vacuo and to the residue cold water was added slowly and the mixture was extracted with ethyl acetate (3 x 200 mL). The combined organic layer was washed with brine (300 mL), dried over Na₂SO₄ and concentrated under vacuo to obtain a crude product. The crude product was purified by combiflash column chromatography using 30-35 % ethylacetate in hexane as an eluent to obtain **3** as a pale yellow solid. (3.5 g, 46 %) ESI-MS(m/z): 412.9 (M + 1); ¹H NMR (400 MHz, CDCl₃): 5.54 (s, 2H); 7.45-7.54 (m, 3H); 7.60-7.62 (m, 1H); 8.15 (s, 1H); 8.21 (s, 1H).

Step 2: 2-chloro-N-(2,2-dimethoxyethyl)-8-[1-[[3-(trifluoromethyl)phenyl]methyl]pyrazol-4-yl]-7H-purin-6-amine

- 15 To a solution of **3** (0.5 g, 1.21 mmol) in NMP (10 mL) was added DIPEA (0.20 mL, 1.21 mmol), and aminoacetaldehyde dimethyl acetal (0.16 mL, 1.45 mmol). The mixture was stirred at 130 °C for 1 h. Reaction completion was confirmed by TLC, then cooled to room temperature and the reaction mixture was slowly poured into water (25 mL) with vigorous stirring. Solid material separated was filtered off, and

washed with cold water (20 mL), followed by n-hexane and dried to obtain **4** as a off white solid (0.4 g, 68%).

MS(ESI)m/z:481.9 (M + 1); ¹H NMR (400 MHz, DMSO-d₆): δ 3.30 (s, 6H); 3.53 (br s, 2H); 4.62 (br s, 1H); 5.56 (s, 2H); 7.58-7.70 (m, 4H); 8.06 (s, 1H); 8.41 (s, 1H);
5 13.30 (br s, 1H).

Step 3: 2-[1-[[3-(trifluoromethyl)phenyl]methyl]pyrazol-4-yl]-1,4-dihydroimidazo[2,1-f]purin-5-one (5)

A mixture of **4** (0.1 g, 0.20 mmol) in conc. H₂SO₄(0.033 mL, 0.60 mmol) was stirred
10 at 70 °C for 16 h. Reaction completion was confirmed by TLC, then cooled to room temperature and the reaction mixture was slowly poured into water (25 mL) with vigorous stirring. Solid material separated was filtered off, and washed with cold water (20 mL), followed by n-hexane and dried to obtain **5** as white solid (0.05 g, 60%)

15 MS(ESI)m/z:400.2 (M + 1); ¹H NMR (400 MHz, DMSO-d₆): δ 5.53 (s, 2H), 7.31 (d, J = 1.6 Hz, 1H); 7.59-7.64 (m, 2H), 7.69-7.71 (m, 2H), 7.73 (d, J = 1.2 Hz, 1H), 8.08 (s, 1H), 8.44 (s, 1H), 12.40 (s, 1H), 13.60 (s, 1H).

Step 4: 2-[1-[[3-(trifluoromethyl)phenyl]methyl]pyrazol-4-yl]-1-(2-trimethylsilylethoxymethyl)-4H-imidazo[2,1-f]purin-5-one (6)

20 To a solution of **5** (1.5 g, 3.75 mmol) in DMF (15 mL) was added K₂CO₃ (1.55 g, 11.27 mmol), and 2-(chloromethoxy)ethyl-trimethyl-silane (4 mL, 22.55 mmol). The mixture was stirred at room temperature for 16 h. Reaction completion was confirmed by TLC then dissolved in water (100 mL), and the mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with
25 brine (100 mL), dried over Na₂SO₄ and concentrated under vacuo to obtain a crude product (1.5 g).

MS(ESI)m/z:530.2 (M + 1); ¹H NMR : Not recorded

Step 5: 4-propyl-2-[1-[[3-(trifluoromethyl)phenyl]methyl]pyrazol-4-yl]-1-(2-trimethylsilylethoxymethyl)imidazo[2,1-f]purin-5-one (7)

30 To a solution **6** (1.5 g, 0.605 mmol) in DMF (15 mL) was added potassium carbonate (0.39 g, 3.83 mmol)and n-propyliodide (0.28 g, 2.83 mmol). The mixture was stirred

at 80 °C for 16 hours. Reaction completion was confirmed by TLC then dissolved in water (100 mL), and the mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄ and concentrated under vacuo to obtain a crude product. The residue was purified by column chromatography using 30-35 % ethyl acetate in hexane as a mobile phase to obtain the title compound **7** (0.5 g).

MS(ESI)m/z: 572.0 (M + 1); ¹H NMR: Not recorded

Step 6: 4-propyl-2-[1-[[3-(trifluoromethyl)phenyl]methyl]pyrazol-4-yl]-1H-imidazo[2,1-f]purin-5-one (8)

A solution of **7** (0.5 g, 0.87 mmol) in ethanol:2N HCl (30 mL) was heated at 80 °C for 16 hours. Reaction completion was confirmed by TLC then cooled to room temperature and concentrated under vacuo to obtain a crude product. The residue was basified by aqueous NaHCO₃ solution up to PH (7-8) then extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄ and concentrated under vacuo to obtain a crude product. The residue was purified by column chromatography using 2-4 % methanol in DCM as a mobile phase to obtain the title compound **8** as a off white solid (0.012 g, 8%).

MS(ESI)m/z: 442.2 (M + 1); ¹H NMR (400 MHz, DMSO-d₆): δ 0.92 (t, *J* = 7.2 Hz, 3H); 1.81 (q, *J* = 6.8 Hz, 2H); 4.18 (t, *J* = 7.2 Hz, 2H); 5.53 (s, 2H); 7.33 (d, *J* = 1.6 Hz, 1H); 7.60-7.70 (m, 4H); 7.76 (d, *J* = 1.2 Hz, 1H); 8.11 (s, 1H); 8.51 (s, 1H); 13.80 (br s, 1H).

The following compounds can also be prepared according to **Schemes 1-5** or in the same manner as in the above-mentioned examples

2-[1-(2-furylmethyl)pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**III**),
5-propyl-2-[1-(2-thienylmethyl)pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (**IV**),
2-[1-(oxazol-2-ylmethyl)pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**V**),
2-[1-(isoxazol-5-ylmethyl)pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**VI**),
2-[1-[(5-methyl-2-thienyl)methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**VII**),

- 2-[1-[(3,5-difluorophenyl)methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**VIII**),
5-propyl-2-[1-(4-pyridylmethyl)pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (**IX**),
5-propyl-2-[1-(3-pyridylmethyl)pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (**X**),
5 5-propyl-2-[1-(2-pyridylmethyl)pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (**XI**),
5-propyl-2-[1-(pyrimidin-5-ylmethyl)pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (**XII**),
5-propyl-2-[1-(pyridazin-4-ylmethyl)pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (**XIII**),
10 2-[1-[(1-oxoisindolin-5-yl)methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XIV**),
2-[1-[(2-methyl-1-oxo-isoindolin-5-yl)methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XV**),
2-[1-[(1-oxo-3,4-dihydro-2H-isoquinolin-6-yl)methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XVI**),
15 2-[1-[(2-oxo-3,4-dihydro-1H-quinolin-6-yl)methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XVII**),
5-propyl-2-[1-(quinoxalin-6-ylmethyl)pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (**XVIII**),
20 2-[1-(2-naphthylmethyl)pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XIX**),
2-[1-[[3-(azetidin-3-yl)phenyl]methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XX**),
2-[1-[[3-(2-methoxyethoxy)phenyl]methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XXI**),
25 2-[1-[[4-(2-methoxyethoxy)phenyl]methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XXII**),
5-propyl-2-[1-[3-[3-(trifluoromethyl)phenyl]prop-2-ynyl]pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (**XXIII**),
30 2-[1-[3-(3-fluorophenyl)prop-2-ynyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XXIV**),

- 2-[1-[3-(4-fluorophenyl)prop-2-ynyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XXV**),
5-propyl-2-[1-[3-[4-(trifluoromethyl)phenyl]prop-2-ynyl]pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (**XXVI**),
5 2-[1-[[1-(3-fluorophenyl)-5-oxo-pyrrolidin-3-yl]methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XXVII**),
2-[1-[[1-(m-tolyl)-5-oxo-pyrrolidin-3-yl]methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XXVIII**),
2-[1-[(3-chloro-5-fluoro-phenyl)methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XXIX**),
10 2-[[4-(4-oxo-5-propyl-3H-imidazo[2,1-b]purin-2-yl)pyrazol-1-yl]methyl]benzonitrile (**XXX**),
2-[1-[(2-fluorophenyl)methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XXXI**),
15 4-[[4-(4-oxo-5-propyl-3H-imidazo[2,1-b]purin-2-yl)pyrazol-1-yl]methyl]benzonitrile (**XXXII**),
2-[1-[[3-(4-methylpiperazin-1-yl)phenyl]methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XXXIII**),
2-[1-[1-(3-fluorophenyl)ethyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XXXIV**),
20 2-[1-[(4-isopropylphenyl)methyl]pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XXXV**),
5-propyl-2-[1-(2,2,2-trifluoroethyl)pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (**XXXVI**),
25 2-[1-(2-aminoethyl)pyrazol-4-yl]-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XXXVII**),
5-propyl-2-(1-tetrahydropyran-4-yl)pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (**XXXVIII**),
2-(1-cyclopentylpyrazol-4-yl)-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XXXIX**),
30 7-methyl-5-propyl-2-[1-[[3-(trifluoromethyl)phenyl]methyl]pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (**XL**),

- 8-methyl-5-propyl-2-[1-[[3-(trifluoromethyl)phenyl]methyl]pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (**XLI**),
- 7-methyl-5-propyl-2-(1-propylpyrazol-4-yl)-3H-imidazo[2,1-b]purin-4-one (**XLII**),
- 2-(1-ethylpyrazol-4-yl)-7-methyl-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XLIII**),
- 5 7-methyl-2-(1-methylpyrazol-4-yl)-5-propyl-3H-imidazo[2,1-b]purin-4-one (**XIV**),
- 5-propyl-2-(1-propylpyrazol-4-yl)-7-(trifluoromethyl)-3H-imidazo[2,1-b]purin-4-one (**XLV**),
- 5-propyl-7-(trifluoromethyl)-2-[1-[[3-(trifluoromethyl)phenyl]methyl]pyrazol-4-yl]-3H-imidazo[2,1-b]purin-4-one (**XLVI**),
- 10 2-[1-(m-tolylmethyl)pyrazol-4-yl]-4-propyl-1H-imidazo[2,1-f]purin-5-one (**XLVII**),
- 2-[1-[(3-fluorophenyl)methyl]pyrazol-4-yl]-4-propyl-1H-imidazo[2,1-f]purin-5-one (**XLVIII**),
- 3-[[4-(5-oxo-4-propyl-1H-imidazo[2,1-f]purin-2-yl)pyrazol-1-yl]methyl]benzonitrile (**XLIX**),
- 15 3-[[4-(4-ethyl-5-oxo-1H-imidazo[2,1-f]purin-2-yl)pyrazol-1-yl]methyl]benzonitrile (**L**),
- 3-[1-methyl-1-[4-(4-oxo-5-propyl-3H-imidazo[2,1-b]purin-2-yl)pyrazol-1-yl]ethyl]benzonitrile (**LI**),
- 20 5-propyl-2-[3-[[3-(trifluoromethyl)phenyl]methoxy]isoxazol-5-yl]-3H-imidazo[2,1-b]purin-4-one (**LII**).

[00154] The compounds of the disclosure may be prepared by a variety of methods, including standard synthetic chemistry. Any previously defined variable will continue to have the previously defined meaning unless otherwise indicated.

25 Illustrative general synthetic methods are set out in the schemes and can be readily adapted to prepare other compounds of the disclosure.

Example 4

Biological Assay

Radioligand Binding for A_{2A} Adenosine Receptor

- 30 **[00155]** Human A_{2A} adenosine receptor cDNA was stably transfected into HEK-293 cells. HEK-A2B cells were harvested by trypsinization with 0.25%

Trypsin-EDTA (Sigma), and washed in 1X PBS at 1500 rpm for 5 minutes at room temperature. The cells were washed twice in wash buffer containing 150 mM NaCl, 1 mM EDTA, 50 mM Tris (pH-7.4) at 1500 rpm for 10 minutes at room temperature and incubated for 10 min at 4 °C in sonication buffer containing 1 mM EDTA, 5 mM
5 (Tris pH 7.4). The cells were sonicated on ice for 6 min with six intermittent pulses of 9 second each and centrifuged at 1000Xg for 10 minutes at 4 °C. The pellet was discarded and the supernatant was centrifuged at 49,000Xg for 45 minutes at 4°C. The protein pellet was resuspended in buffer containing 1 mM EDTA, 5 mM Tris (pH-7.4) supplemented with 1 Unit/ml adenosine deaminase (ADA) and incubated
10 for 30 minutes at room temperature. The lysate was washed twice with buffer containing 1 mM EDTA, 5 mM Tris (pH-7.4) at 49,000Xg for 45 minutes at 4 °C and the protein pellet was resuspended in 50 mM Tris, pH-7.4 supplemented with 1 Unit/ml ADA and 10% sucrose. Frozen aliquots were stored at -80°C.

[00156] Competition assays were started by mixing 2 nM [³H]-ZM-241385 with
15 various concentrations of test compounds and 5 µg membrane protein in Reaction buffer (50 mM Tris pH 7.4, 1 mM EDTA) supplemented with 1 Unit/ml ADA. The assay reactions were incubated for 90 minutes at room temperature and stopped by filtration using 96 well-plate harvester (Molecular Devices) and washed four times with ice cold 50 mM Tris (pH 7.4). Non-specific binding was determined in presence
20 of 200 µM NECA. Radioligand binding was read at Liquid scintillation counter (Perkin Elmer) and the affinities of compounds (i.e. K_i values) were calculated using GraphPad software.

[00157] Compounds tested had micromolar to nanomolar activity.

Radioligand Binding for A_{2B} Adenosine Receptor

[00158] Human A_{2B} adenosine receptor cDNA was stably transfected into HEK-
25 293 cells. HEK-A2B cells were harvested by trypsinization with 0.25% Trypsin-EDTA (Sigma) and washed in 1X PBS at 1500 rpm for 5 minutes at room temperature. The cells were washed twice in wash buffer containing 150 mM NaCl, 1 mM EDTA, 50 mM Tris (pH-7.4) at 1500 rpm for 10 minutes at room temperature
30 and incubated for 10 min at 4°C in sonication buffer containing 1 mM EDTA, 5 mM Tris (pH 7.4). The cells were sonicated on ice for 6 min with six intermittent pulses

of 9 second each and centrifuged at 1000Xg for 10 minutes at 4°C. The pellet was discarded, and the supernatant was centrifuged at 49,000Xg for 45 minutes at 4°C. The protein pellet was resuspended in buffer containing 1 mM EDTA, 5 mM Tris (pH-7.4), 1 Unit/ml adenosine deaminase (ADA) and incubated for 30 minutes at
5 room temperature. The lysate was washed twice with buffer containing 1 mM EDTA, 5 mM Tris (pH-7.4) at 49,000Xg for 45 minutes at 4°C and the protein pellet was resuspended in 50 mM Tris, pH-7.4 supplemented with 1 Unit/ml ADA and 10% sucrose. Frozen aliquots were stored at -80°C.

[00159] Competition assays were started by mixing 1.6 nM [³H]-MRS-1754 with
10 various concentrations of test compounds and 10 µg membrane protein in Reaction buffer (50 mM Tris pH 6.5, 5 mM MgCl₂, 1 mM EDTA) supplemented with 1U/ml Adenosine deaminase. The assay reactions were incubated for 90 minutes at room temperature and stopped by filtration using 96 well-plate harvester (Molecular Devices) and washed four times with ice cold 50 mM Tris (pH 7.4). Non-specific
15 binding was determined in presence of 200 µM NECA. Radioligand binding was read at Liquid scintillation counter (Perkin Elmer) and the affinities of compounds (i.e. K_i values) were calculated using GraphPad software.

[00160] Compounds tested had micromolar to nanomolar activity.

cAMP Assay for Adenosine Receptor.

[00161] The functional activity of test compounds on A_{2A} and A_{2B} adenosine
20 receptors and selectivity over A₁ adenosine was determined using HTRF based cAMP assay (Cisbio). Briefly, overnight seeded cultures (HEK-A₁, HEK-A_{2A}, HEK-A_{2B}) were treated with 1U/ml ADA for 90 minutes at 37°C and 5% CO₂. Cell suspensions were treated with increasing concentrations of test compounds for 15
25 minutes followed by treatment with agonists for 15 minutes (1nM CPA for HEK-A₁ and 70 nM NECA for HEK-A_{2B}) or 30 min (10 nM CGS-21680 for HEK-A_{2A}) at room temperature with continuous mixing in incomplete DMEM supplemented with 1U/ml ADA. Rolipram (20 µM) was included in the assay for A₁ and A_{2A} adenosine
30 receptors. For functional activity of HEK-A₁, cell suspensions were further treated with forskolin for 30 minutes at room temperature with constant mixing. cAMP levels were quantified using a Flex Station III (Molecular Devices) at an excitation

maximum of 313 nm and emission maxima of 620 nm and 665 nm. Data was analyzed using GraphPad Prism to generate IC₅₀ and K_i. The biological activity data is provided in the Table below. <10 nM are represented as +++++, 10-30 nM as +++, 30-100 nM ++ and the K_i value >100 nM as +.

Ex.No.	A2A Functional K _i nM	A2B Functional K _i nM
A1	+++++	+++++
A2	ND	ND
A3	+++	+++++
A4	ND	ND
A5	++	ND
A6	+	ND
A7	+++++	+++++
B2	+++	+++++
B3	+++	+++++
B6	++	+++++
B7	+++++	+++++
B8	+++	+++++
B9	+++	+++++
B10	+++	+++++
B11	+	+++
B12	+	+++
B13	+++++	+++++
B14	+	+++++
B16	+++++	+++++
B17	+++	+++++
B19	+++++	+++++
B20	+++++	+++++
C2	++	+++++
D1	++	+++++
E1	+++++	+++++
F1	+++	+++++
G1	+++	+++++
H1	+	++
J1	++	++
N3	+++++	+++++
N4	+++++	+++++
N5	++	+++

5 ND= NOT DETERMINED

[00162] Although the subject matter has been described in considerable detail with reference to certain preferred embodiments thereof, other embodiments are possible.

As such, the spirit and scope of the appended claims should not be limited to the description of the preferred embodiment contained therein.