

PURINE DIONES AS WNT PATHWAY MODULATORS

Field

[0001] The invention relates to Wnt pathway modulators, processes for making them and methods for using them.

Background

[0002] The present application claims priority from application GB1309333.1, filed on 23 May 2013, the entire contents of which are incorporated herein by cross-reference.

[0003] Wnt proteins are secreted glycoproteins acting as growth factors that regulate various cellular functions, including proliferation, differentiation, death, migration, and polarity, by activating multiple intracellular signalling cascades, including the β -catenin-dependent and – independent pathways. There are 19 Wnt members that have been found in humans and mice, and they exhibit unique expression patterns and distinct functions during development. In humans and mice, the 10 members of the Frizzled (Fz) family comprise a series of seven-pass transmembrane receptors that have been identified as Wnt receptors. In addition to Fz proteins, single-pass transmembrane proteins, such as low-density lipoprotein receptor-related protein 5 (LRP5), LRP6, receptor tyrosine kinase (RTK)-like orphan receptor 1 (Ror1), Ror2, and receptor-like tyrosine kinase (Ryk), have been shown to function as co-receptors for Wnt signalling. Therefore, it has been assumed traditionally that the binding of different Wnts to their specific receptors selectively triggers different outcomes via distinct intracellular pathways.

[0004] In the absence of Wnt signalling, β -catenin is bound and phosphorylated by a “destruction complex” containing the adenomatous polyposis coli (APC) and Axin proteins, as well as glycogen synthase kinase 3 (GSK3) and casein kinase I (CKI). Phosphorylated β -catenin is bound by the F box protein Slimb/ β -TrCP and polyubiquitinated, leading to proteosomal degradation. In addition, the complex acts to prevent nuclear localization of β -catenin. Upon Wnt binding to Frizzled (Fz) and low-density lipoprotein-related proteins 5 and 6 (LRP5/6), GSK3, Axin, and other destruction complex components are recruited to the receptor complex. The function of the destruction complex is inhibited, and unphosphorylated β -catenin accumulates in the cytoplasm and eventually translocates to the nucleus. There, it associates

with TCF proteins, converting TCF from a repressor into an activator of Wnt-responsive gene transcription.

[0005] Deregulation of components of Wnt/ β -catenin signalling is implicated in a wide spectrum of diseases including degenerative diseases, metabolic diseases, and a number of cancers such as cervical, colon, breast, bladder, head and neck, gastric, lung, ovarian, prostate, thyroid, non-small-cell lung, as well as chronic lymphocytic leukemia, mesothelioma, melanoma, pancreatic adenocarcinoma, basal cell carcinoma, osteosarcoma, hepatocellular carcinoma, Wilm's tumor and medulloblastoma. Wnt signalling plays a role both during development, and within stem cell niches in adults. This is best established in skin, hematopoietic stem cells, mammary gland and in intestinal proliferation. For example, high level expression of DKK1, an inhibitor of Wnt signalling, blocks normal stem cell proliferation in mouse intestines, suggesting there is an essential role for Wnt signalling in maintenance of stem cells in the digestive tract. The role of Wnt in self renewal and expansion of stem cells has also been demonstrated for embryonic and neural stem cells, suggesting that Wnt signalling may be a general requirement of stem cell maintenance.

[0006] Inhibition of Wnt signalling, e.g., by overexpression of axin or an extracellular Wnt-binding protein, sFRP, reduces hematopoietic stem cell (HSC) growth in vitro and the ability to reconstitute HSCs in vivo. Notably, while overexpression of activated β -catenin can expand HSC populations in culture for extended periods, two groups have reported that β -catenin is not required for HSC survival and serial transplantation, supporting the proposal that there is more to Wnt signalling than stabilization of β -catenin in stem cell survival. Diverse Wnts can regulate stem cell proliferation: Wnts 1, 5a, and 10b are able to stimulate expansion of HSC populations and Wnt5a acts synergistically with stem cell factor (SCF) to expand and promote self-renewal of HSCs. The demonstration of a role for Wnt5a in HSC self-renewal and its ability to synergize with stem cell factor is particularly interesting because Wnt5a often acts in a β -catenin independent manner. While Wnt signalling is critical for stem cell maintenance, it may therefore be via signalling pathways distinct from or in parallel to the β -catenin pathway.

[0007] Wnt/ β -catenin signalling pathway is essential to embryonic development in general and organ morphogenesis, so it is not surprising that dysregulation of this pathway in adult has been linked to fibroblast biology and fibrosis. It has been demonstrated that Wnt/ β -catenin signalling

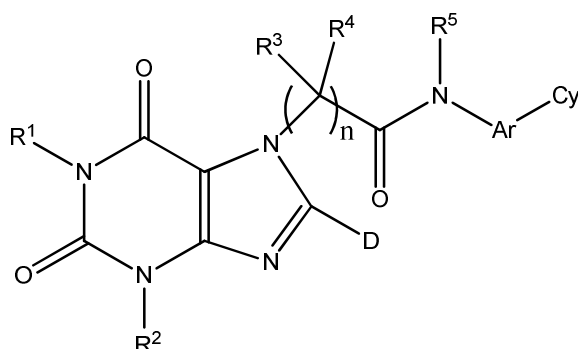
play a role in severe fibrotic diseases, such as pulmonary fibrosis, liver fibrosis, skin fibrosis and renal fibrosis.

[0008] Dysregulation of Wnt/ β -catenin signalling contributes also to the development of diabetic retinopathy by inducing retinal inflammation, vascular leakage, and neovascularization. The binding of Wnt proteins to plasma membrane receptors on mesenchymal cells induces the differentiation of these cells into the osteoblast lineage and thereby supports bone formation. Wnts are also key signalling proteins in joint remodeling processes. Active Wnt signalling contributes to osteophyte formation and might have an essential role in the anabolic pattern of joint remodeling that is observed in ankylosing spondylitis and osteoarthritis. In contrast, blockade of Wnt signalling facilitates bone erosion and contributes to catabolic joint remodeling, a process that is observed in rheumatoid arthritis.

[0009] There is therefore a need for compounds that modulate or inhibit Wnt activity so as to treat diseases associated with Wnt activity.

Summary

[00010] There is provided a compound of structure (I) for use in, or when used in, modulating Wnt activity,



(I)

wherein:

R^1 , R^2 , R^3 , R^4 and R^5 are each, independently, H or an alkyl group;

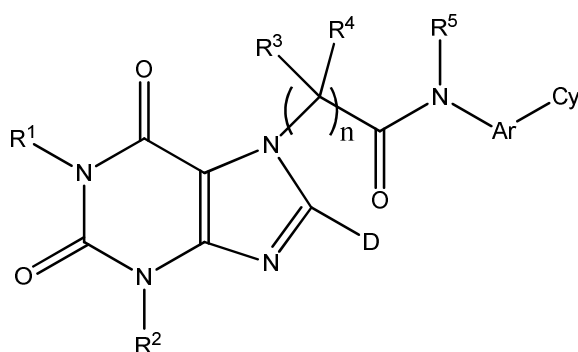
D is selected from the group consisting of H, halogen, alkyl, cycloalkyl, aryl, and dialkylamino, each (other than H and halogen) being optionally substituted;

Ar is an aryl or heteroaryl group, each being optionally substituted;

Cy is an aryl, heteroaryl or a saturated ring containing at least one heteroatom, each being optionally substituted; and

n is an integer from 1 to 3.

[00010a] In an aspect, there is provided a compound having structure (I)



(I)

wherein:

R^1 , R^2 , R^3 , R^4 and R^5 are each, independently, H or an alkyl group;

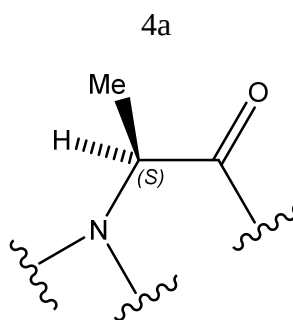
D is selected from the group consisting of H, halogen, alkyl, cycloalkyl, aryl, and dialkylamino, each (other than H and halogen) being optionally substituted;

Ar is a 6-membered heteroaryl ring having 1 or 2 nitrogen atoms having no substituents other than Cy and the amide nitrogen atom, these being in a 1,4-relationship on said ring; and

Cy is an aryl, heteroaryl or a saturated ring containing at least one heteroatom, each being optionally substituted; and

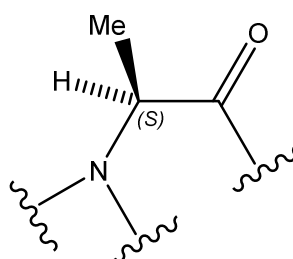
n is an integer from 1 to 3

wherein, if $n=1$ and one of R^3 and R^4 is methyl and the other is H, the stereochemistry of the compound is as shown in partial structure (II):



(II).

[00011] In some embodiments, if $n=1$ and one of R^3 and R^4 is methyl and the other is H, the stereochemistry of the compound is as shown in partial structure (II)

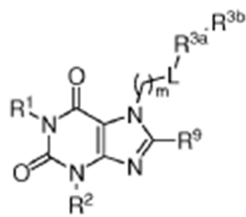


(II).

In some particular embodiments, $n=1$ and one of R^3 and R^4 is methyl and the other is H and the stereochemistry of the compound is as shown in partial structure (II).

[00012] Any one or more of the following groups a) to e), and/or any one or more individual compounds within any one or more of said groups, optionally all thereof, may be excluded from the scope of the first aspect. Notwithstanding any such exclusions, the compounds referred to hereinafter as compound 5 and compound 86 may be explicitly included within the scope of the first aspect.

- a) Any one or more of the compounds described in WO2010/036821 A1;
- b) Any one or more compounds of the formula shown below,



wherein, R¹ and R² are each independently C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl, each of which is optionally substituted with 1-4 R⁵; L is NR⁶SO₂, SO₂NR⁶, OC(O)NR⁶, NR⁶C(O)O, NR⁶C(O)NR⁶, NR⁶C(O), C(O)NR⁶, O, C(O), S, S(O), S(O)₂, NR₆, or CH₂, each of R^{3a} and R^{3b} is independently cyclyl, heterocyclyl, aryl, heteroaryl, each of which is optionally substituted with 1-4 R⁷; each R⁵ is independently halo, hydroxyl, alkoxy, amino, alkylamino, dialkylamino, cyano, nitro, amido (e.g., where the nitrogen of the amide is substituted by an alkyl, or where the nitrogen of the amide together with two carbons to which it is attached, forms a ring), alkylamido, dialkylamido, thioyl, sulfonyl, cyclyl, heterocyclyl, aryl, or heteroaryl; each R⁶ is independently H, C₁-C₆ alkyl, C₁-C₆ alkenyl, hydroxyC₁-C₆ alkyl, alkoxyC₁-C₆ alkyl, cyanoalkyl, haloalkyl, arylalkyl, S(O)alkyl, acyl, amino, amidyl, or S(O)₂H, aryl, alkoxyaryl; each R⁷ is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl, halo, hydroxyl, alkoxy, oxo, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, aryloxy, arylalkoxy, amino, alkylamino, dialkylamino, thioyl, alkylthioyl, sulfonyl, sulfonamidyl, amido (e.g., where the nitrogen of the amide is substituted by an alkyl, or where the nitrogen of the amide together with two carbons to which it is attached, forms a ring), hydroxyl alkoxy, alkoxy -C(O)OH, -C(O)Oalkyl, urea, sulfonylurea, acyl, nitro, cyano, each of which is optionally substituted with 1-3 R⁸; each R⁸ is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl, aryl, heteroaryl, cyclyl, halo, hydroxyl, alkoxy, oxo, aryloxy, amino, alkylamino, dialkylamino, C(O)OH, -C(O)Oalkyl, thioyl, sulfonyl, sulfonamidyl, amido (e.g., where the nitrogen of the amide is substituted by an alkyl, or where the nitrogen of the amide together with two carbons to which it is attached, forms a ring), urea, sulfonylurea, acyl, nitro, cyano, cyclyl, heterocyclyl, aryl, or heteroaryl; R⁹ is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl, halo, C₁-C₆ haloalkyl, hydroxyl, alkoxy, aryloxy, arylalkoxy, amino, alkylamino, dialkylamino, thioyl, alkylthioyl, sulfonyl, sulfonamidyl, amido, urea, sulfonylurea, acyl, nitro, cyano, each of which is optionally substituted with 1-3 R⁸; m is 1, 2, 3, 4, 5, or 6.

c) Any one or more compounds of structure I wherein R¹ and R² are both methyl, D, R³, R⁴ and R⁵ are all H, n is 1 and Ar-Cy is 4-phenylthiazole-2-yl, 4-(4-bromophenyl)thiazole-2-yl, 2- or 4-(N-morpholinyl)phenyl, 4-(N-piperidiny)phenyl, 1-phenyl-3-methylpyrazole-5-yl, 4-(3,4-dimethylphenyl)thiazole-2-yl, 4-(4-ethylphenyl)thiazole-2-yl, 4-(2,4,6-trimethylphenyl)thiazole-

2-yl, 4-(4-n-propylphenyl)thiazole-2-yl, 4-(4-chlorophenyl)-5-methylthiazole-2-yl, 4-phenylphenyl, 2-(N-pyrrolidiny)phenyl, 4-(N-azacycloheptyl)phenyl, 4-(4-bromophenyl)-5-trifluoromethylpyrimidine-2-yl, 4-(2,4-dimethylphenyl)thiazole-2-yl, 4-(3,4-dimethoxyphenyl)thiazole-2-yl, 4-(2-fluorophenyl)thiazole-2-yl, 4-(3,4-difluorophenyl)-5-methylthiazole-2-yl, 4-(4-methoxy-1-naphthyl)thiazole-2-yl, 4-(3-chloro-4-methoxyphenyl)thiazole-2-yl, 4-(4-ethoxyphenyl)-5-methylthiazole-2-yl, 4-(2-acetamido-4-fluorophenyl)thiazole-2-yl, 4-(3-fluoro-4-methoxyphenyl)thiazole-2-yl, 4-(4-bromophenyl)-5-methylthiazole-2-yl, 4-(4-(2-methoxyethyl)phenyl)thiazole-2-yl, 4-(4-methyl-3-nitrophenyl)thiazole-2-yl, 4-phenyl-5-(1-methyl-imidazole-2-yl)thiazole-2-yl, 4-(4-(difluoromethoxy)phenyl)-5-methylthiazole-2-yl, 4-(2,5-diethoxyphenyl)thiazole-2-yl, 4-(4-fluoromethylphenyl)-5-methylthiazole-2-yl, 4-phenyl-5-acetylthiazole-2-yl, 4-(3-chloro-4-fluorophenyl)thiazole-2-yl, 4-(3-fluorophenyl)thiazole-2-yl, 4-(3-methoxyphenyl)thiazole-2-yl, 4-(2-ethoxyphenyl)thiazole-2-yl, 4-(3-chlorophenyl)thiazole-2-yl, 4-(2-methoxyphenyl)thiazole-2-yl, 4-(2-bromophenyl)thiazole-2-yl, 4-(4-diethylaminophenyl)thiazole-2-yl, 4-(2-chlorophenyl)thiazole-2-yl, 4-(4-methoxyphenyl)thiazole-2-yl, 4-(3-bromophenyl)thiazole-2-yl, 4-(4-isopropoxyphenyl)thiazole-2-yl, 4-(2,3,4-trichlorophenyl)thiazole-2-yl, 4-(3-chloro-4-ethoxyphenyl)thiazole-2-yl, 4-(4-chloro-3-fluorophenyl)thiazole-2-yl, 4-(3-ethoxyphenyl)thiazole-2-yl, 4-(2, 4-dimethoxyphenyl)thiazole-2-yl, 4-(2, 4-dimethylphenyl)thiazole-2-yl, 4-(4-ethylphenyl)thiazole-2-yl, 4-(2-methylphenyl)thiazole-2-yl, 4-(2-bromo-5-ethoxyphenyl)thiazole-2-yl, 4-(5-bromo-2-chloro-4-ethoxyphenyl)thiazole-2-yl, 4-(2-chloro-4-ethoxyphenyl)thiazole-2-yl, 4-(3-pyridyl)thiazole-2-yl, 4-(4-(2-hydroxyethoxy)phenyl)thiazole-2-yl, 4-(3-(2-hydroxyethoxy)phenyl)thiazole-2-yl, 4-(2,6-dichlorophenyl)thiazole-2-yl, 4-(3-methylphenyl)thiazole-2-yl, 4,5-bis(4-methylphenyl)oxazole-2-yl, 4,5-diphenyloxazole-2-yl, 4-(4-pyridyl)thiazole-2-yl, 4-(2-(2-hydroxyethoxy)phenyl)thiazole-2-yl, 4-(3,4-dichlorophenyl)-5-methylthiazole-2-yl, 4-(2,4,6-trichlorophenyl)thiazole-2-yl, 4-(4-ethoxyphenyl)-5-phenylthiazole-2-yl, 4-(4-chloro-3-ethoxyphenyl)thiazole-2-yl, 4-(3,4,5-trichlorophenyl)thiazole-2-yl, 5-(4-pyridyl)1,3,4-thiadiazole-2-yl, 4-(3-bromo-6-(2-hydroxyethoxy)phenyl)thiazole-2-yl, 3-(benzoxazole-2-yl)-2-methylphenyl, 4-(3,4-dichlorophenyl)-5-ethylthiazole-2-yl, 4-((3-trifluoromethyl)phenyl)thiazole-2-yl, 4-(2,3-dichlorophenyl)-5-phenylthiazole-2-yl, 4-(2,3-dichlorophenyl)-5-(4-methylphenyl)thiazole-2-yl, 1-phenyl-3-(4-methylphenyl)pyrazole-5-yl, 4,5-bis(3,4-dichlorophenyl)thiazole-2-yl, 5-phenylthiazole-2-yl, 4-(4-(trifluoromethyl)phenyl)thiazole-2-yl, 4-(4-(methylsulfinyl)phenyl)thiazole-2-yl, 4-(4-chlorophenyl)oxazole-2-yl, 4-((4-trifluoromethoxy)phenyl)thiazole-2-yl, 3-(4-

chlorophenyl)pyrazole-5-yl, 3-(4-chlorophenyl)1,3,4-oxadiazole-5-yl, 3-phenylpyrazole-5-yl, 5-(4-methylphenyl)thiazole-2-yl, 4-(4-chlorophenyl)-5-ethylthiazole-2-yl, 4-(4-nitrophenyl)thiazole-2-yl, 4-(4-aminophenyl)thiazole-2-yl, 4-(4-ethoxyphenyl)-5-methyloxazole-2-yl, 4-(4-dimethylamino-3-fluorophenyl)thiazole-2-yl, 3-(thiophene-2-yl)pyrazole-5-yl, 3-(furan-2-yl)pyrazole-5-yl, 4-(4-chlorophenyl)-5-fluorothiazole-2-yl, 2-(pyrrole-N-yl)phenyl, 2-(indole-2-yl)phenyl, 4-(2-hydroxybenzimidazole-5-yl)thiazole-2-yl, 2-(4-chlorophenyl)-4-pyridyl, 3-(4-chlorophenyl)phenyl, 4-(3-chloro-4-dimethylaminophenyl)thiazole-2-yl, 4-(4-ethoxyphenyl)thiazole-2-yl, 5-(4-chlorophenyl)-3-pyridyl, 4-(3,4-dichlorophenyl)-5-isopropylthiazole-2-yl, 4-(4-dimethylamino-2-fluorophenyl)thiazole-2-yl, 4-(4-(tetrahydropyrrole-N-yl)-3-bromophenyl)thiazole-2-yl, 4-(4-fluoro-3-(morpholine-N-yl)phenyl)thiazole-2-yl, 5-(4-chlorophenyl)pyrazole-2-yl, 4-(2,4,5-trichlorophenyl)thiazole-2-yl, 4-(4-diethylaminophenyl)thiazole-2-yl, 4-(2,3-dihydrobenzofuran-5-yl)thiazole-2-yl, 2-(3,4-dichlorophenyl)thiazole-4-yl, 3-phenyl-4-(4-ethoxyphenyl)imidazole-2-yl, 4-(piperidine-N-ylphenyl)thiazole-2-yl, 4-(morpholine-N-ylphenyl)thiazole-2-yl, 4-(3-diethylaminophenyl)thiazole-2-yl, 2-(benzothiazole-2-yl)phenyl, 4-(3-ethylpropylaminophenyl)thiazole-2-yl, 4-(3-dimethylaminophenyl)thiazole-2-yl, 4-(4-chlorophenyl)pyridine-2-yl, 3-(4-diethylaminophenyl)phenyl, 4-(4-ethoxyphenyl)imidazole-2-yl, 4-(N-acetyl-2,3-dihydroindole-5-yl)thiazole-2-yl, 4-(3,4-dichlorophenyl)pyrimidine-2-yl, 3-(thiazole-2-yl)phenyl, 4-(quinoline-2-yl)thiazole-2-yl, 4-(benzothiophene-2-yl)thiazole-2-yl, 4-(isoquinoline-3-yl)thiazole-2-yl, 4-(4-dimethylamino-3,5-difluorophenyl)thiazole-2-yl, 4-(3-(pyrrolidine-N-yl)phenyl)thiazole-2-yl, 4-(4-(aminocarbonylamino)phenyl)thiazole-2-yl, 4-(4-chlorophenyl)-5-methoxythiazole-2-yl, 4-(4-diethylsulfonamidophenyl)thiazole-2-yl, 4-(4-dimethylsulfonamidophenyl)thiazole-2-yl, 4-(2,3-dihydro-1,4-benzoxazine-3-one-6-yl)thiazole-2-yl, 4-(3,4-dichlorophenyl)imidazole-2-yl, 4-(4-ethoxyphenyl)oxazole-2-yl, 4-(4-chlorophenyl)oxazole-2-yl, 3-(4-ethylthiazole-2-yl)phenyl, 3-(5-ethylthiazole-2-yl)phenyl, 3-(4-methylthiazole-2-yl)phenyl, 4-(2-chloro-4-diethylaminophenyl)thiazole-2-yl, 4-(2,5-difluoro-4-diethylaminophenyl)thiazole-2-yl, 4-(3-trifluoromethoxyphenyl)thiazole-2-yl, 6-(4-chlorophenyl)pyridine-2-yl, 3-(4-diethylamino-3-fluorophenyl)phenyl, 4-(4-dimethylamino-2,3-difluorophenyl)thiazole-2-yl, 4-(4-(piperidine-N-ylsulfonyl)phenyl)thiazole-2-yl, 4-(N-acetylindole-5-yl)thiazole-2-yl, 1-phenylmethyl-4-(3,4-dichlorophenyl)imidazole-2-yl, 4-(N-ethyl-2,3-dihydroindole-5-yl)thiazole-2-yl, 3-(4-chlorophenyl)1,2,4-thiadiazole-5-yl, 4-(N-acetyl-2,3-dihydroindole-5-yl)thiazole-2-yl, 4-(N-ethylindole-5-yl)thiazole-2-yl, 1-(4-chlorophenyl)1,2,4-triazole-3-yl, 1-phenylpyrazole-4-yl, 4-(N-acetylindole-6-yl)thiazole-2-yl, 1-(4-chlorophenyl)pyrazole-4-yl, 4-(N-methyl-2,3-dihydroindole-5-yl)thiazole-2-yl, 4-(2-chloro-

4-dimethylamino-5-fluorophenyl)thiazole-2-yl, 4-(3-(N,N-dimethylsulfonamido)thiazole-2-yl, 4-(3-(N,N-diethylsulfonamido)thiazole-2-yl, 2-(4-chlorophenyl)1,3,5-triazine-6-yl, 4-(4-(N-morpholino)sulfonylphenyl)thiazole-2-yl, 4-(4-(N-pyrrolidino)sulfonylphenyl)thiazole-2-yl, 4-(4-chloro-3-diethylaminophenyl)thiazole-2-yl, 4-(4-chloro-3-trifluoromethylphenyl)thiazole-2-yl, 1-ethyl-4-(3,4-dichlorophenyl)imidazole-2-yl, 1-methyl-4-(3,4-dichlorophenyl)imidazole-2-yl, 2-(1-naphthyl)-6-pyridyl, 2-(1-(3,4-dichlorophenyl)-6-pyridyl, 4-(4-chlorophenyl)-5-dimethylaminomethylthiazole-2-yl, 4-(3-diethylaminophenyl)thiazole-2-yl, 4-(3-fluoro-4-diethylaminophenyl)-5-ethylthiazole-2-yl, 4-(4-chlorophenyl)-5-(2-dimethylaminoethyl)thiazole-2-yl, 4-(2-fluoro-4-trifluoromethylphenyl)thiazole-2-yl, 4-(3-fluoro-5-trifluoromethylphenyl)thiazole-2-yl, 4-(3-fluoro-4-trifluoromethylphenyl)thiazole-2-yl, 4-(4-fluoro-3-trifluoromethylphenyl)thiazole-2-yl, 4-(3,4-dichlorophenyl)-5-methoxycarbonylmethylthiazole-2-yl, 1,5-dimethyl-4-(3,4-dichlorophenyl)imidazole-2-yl, N-(4-chlorophenyl)pyrrole-3-yl, 4-(3,4-dichlorophenyl)-5-aminocarbonylthiazole-2-yl, 4-(2-ethoxynaphth-6-yl)thiazole-2-yl, 4-(3,4-dichlorophenyl)-5-hydroxycarbonylmethylthiazole-2-yl, 4-(4-diethylamino-2,5-difluorophenyl)-5-methylthiazole-2-yl, 4-(4-(N-pyrrolidino)-3-fluorophenyl)thiazole-3-yl, 4-(4-diethylamino-3-ethoxyphenyl)thiazole-3-yl, 4-(4-diethylamino-2-ethoxyphenyl)thiazole-3-yl, 4-(4-(N-pyrrolidino)-3-trifluoromethylphenyl)thiazole-3-yl, 4-(4-diethylamino-3-trifluoromethylphenyl)thiazole-3-yl, 1-n-butyl-4-(3,4-dichlorophenyl)imidazole-2-yl, 1-(4-chlorophenyl)imidazole-4-yl, 5-(4-chlorophenyl)1,2,4-oxadiazole-3-yl, 4-phenyl-5-(4-ethoxyphenyl)oxazole-2-yl, 2-(2-naphthyl)pyridine-6-yl, 4-(4-methoxycarbonylphenyl)thiazole-2-yl, 4-(3-(methylethylamino)phenyl)-5-methylthiazole-2-yl, 4-(3-diethylamino-4-ethoxyphenyl)thiazole-2-yl, 4-(4-diethylaminophenyl)-5-fluorothiazole-2-yl, 4-(4-(N-ethylpiperazine-N'-yl)-3-trifluoromethylphenyl)thiazole-2-yl, 4-(3-ethoxycarbonylphenyl)thiazole-2-yl, 4-(3,5-difluoro-4-(N-pyrrolidino)phenyl)thiazol-2-yl, 4-(4-chlorophenyl)-5-trifluoromethylthiazole-2-yl, 4-(3-cyano-4-(methylethylamino)phenyl)thiazole-2-yl, 4-(2-ethoxynaphth-5-yl)thiazole-2-yl, 5-(4-chloromethylphenyl)isothiazole-3-yl, 4-(N-methylindole-5-yl)thiazole-2-yl, 4-(3,4-trichlorophenyl)-5-(2-hydroxyethyl)thiazole-2-yl, 2-(4-chlorophenyl)imidazole-4-yl, 1-(4-chlorophenyl)1,2,3-triazole-4-yl, 4-(4-(N-imidazolyl)phenyl)thiazole-2-yl, 4-(4-(N-tetrazolyl)phenyl)thiazole-2-yl, 4-(4-(4-methoxyphenyl)methylaminophenyl)thiazole-2-yl, 4-(4-(N-pyrrolidinyl)-3,5-difluorophenyl)-5-fluorothiazole-2-yl, 4-(4-(N-morpholino)-3-trifluoromethylphenyl)thiazole-2-yl, 4-(4-(N-piperidinyl)-3-trifluoromethylphenyl)thiazole-2-yl, 4-(4-nitrophenyl)-5-trifluoromethylthiazole-2-yl, 4-(4-dimethylamino-3-trifluoromethylphenyl)-5-trifluoromethylthiazole-2-yl, 4-(3-hydroxycarbonylphenyl)thiazole-2-yl, 4-(4-hydroxycarbonylphenyl)thiazole-2-yl, 4-(2,5-

difluoro-4-(N-pyrrolidinyl)phenylthiazole-2-yl, 4-(4-diethylamino-3-fluorophenyl)-5-fluorothiazole-2-yl, 4-(4-aminophenyl)-5-trifluoromethylthiazole-2-yl, 4-(4-(N-pyrrolidino)phenyl)thiazole-2-yl, 4-(2,5-difluoro-4-(N-ethylpiperazine-N'-yl)phenyl)thiazole-2-yl, 4-(4-diethylaminophenyl)-5-trifluoromethylthiazole-2-yl, 4-(3,5-difluoro-4-diethylaminophenyl)-5-fluorothiazole-2-yl, 4-(4-(N-morpholinyl)-2,5-difluorophenyl)thiazole-2-yl, 4-(4-(N-piperidinyl)-2,5-difluorophenyl)thiazole-2-yl, 4-(4-(N-pyrazolyl)-3-fluorophenyl)thiazole-2-yl, 4-(4-chlorophenyl)-5-methylthiazole-2-yl, 5-methylthiazole-2-ylphenyl, 4-(1-ethoxynaphth-3-yl)thiazole-2-yl, 3-(4-chlorophenyl)isothiazole-5-yl, 4-(benzofuran-5-yl)thiazole-2-yl, 3-(4-chlorophenyl)isoxazole-5-yl, 4-(3-(N-pyrrolidinocarbonyl)phenyl)thiazole-2-yl, 4-(4-dimethylaminophenyl)-5-phenylthiazole-2-yl, 4-(3-(N-morpholinocarbonyl)phenyl)thiazole-2-yl, 4-(4-diethylaminophenyl)-5-trifluoroacetylthiazole-2-yl, 4-(4-diethylamino-3-fluorophenyl)-5-trifluoromethylthiazole-2-yl, 4-(4-ethylamino-3-fluorophenyl)-5-trifluoromethylthiazole-2-yl, 4-(4-diethylamino-3-fluoro-5-trifluoromethylphenyl)-5-trifluoromethylthiazole-2-yl, 4-(4-(2-dimethylaminoethoxy)-3-fluorophenyl)thiazole-2-yl, 4-(4-N-(pyrrolindinyl)phenyl)-5-ethylthiazole-2-yl, 2-(4-(N-pyrrolidinyl)-3-fluorophenyl)pyridine-6-yl, 4-(4-fluoro-3-(N-pyrrolidinyl)phenyl)thiazole-2-yl, 4-(3-(N-pyrrolidinyl)-4-diethylaminophenyl)thiazole-2-yl, 4-(4-(N-pyrrolyl)phenyl)-5-trifluoromethylthiazole-2-yl, 2-(4-chlorophenyl)thiophene-5-yl, 4-(1-ethoxynaphth-5-yl)thiazole-2-yl, 1-(4-chlorophenyl)pyrazole-3-yl, 4-(4-(N-pyrrolidinyl)-2,5-difluorophenyl)-5-ethylthiazole-2-yl, 4-(4-(N-pyrrolidinyl)-3-trifluoromethylphenyl)-5-methylthiazole-2-yl, 4-(4-(N-piperidinyl)-3-trifluoromethylphenyl)-5-methylthiazole-2-yl, 4-(4-chlorophenyl)-5-n-propylthiazole-2-yl, 4-(4-ethoxy-2-(N-pyrrolidinyl)phenyl)thiazole-2-yl, 4-(4-chloro-2-(N-pyrrolidinyl)phenyl)thiazole-2-yl, 4-(4-(N-pyrrolidinyl)phenyl)-5-fluorothiazole-2-yl, 4-(2-chloropyridine-5-yl)thiazole-2-yl, 2-(4-(N-pyrrolidinyl)phenyl)pyridine-6-yl, 4-(4-(N-pyrrolidinyl)-3-fluorophenyl)-5-ethylthiazole-2-yl, 4-(2-chloropyrid-3-yl)thiazole-2-yl, 4-(4-(2-methyl-N-pyrrolidinyl)-3-fluorophenyl)thiazole-2-yl, 4-(4-(N-pyrrolidinyl)-3-trifluoromethylphenyl)-5-methylthiazole-2-yl, 4-(4-diethylamino-2-chlorophenyl)-5-ethylthiazole-2-yl, 5-(4-chlorophenyl)-4-ethylthiazole-2-yl, 4-(3,4-dichlorophenyl)-5-aminothiazole-2-yl, 4-(6-chloroquinoline-3-yl)thiazole-2-yl, 4-(2,4-bis(N-pyrrolidinyl)phenyl)thiazole-2-yl, 4-(4-(2,4-dimethylpyrrolidine-N-yl)phenyl)-3-fluorothiazole-2-yl, 4-(thionaphthene-3-yl)thiazole-2-yl, 4-(4-diethylaminophenyl)-5-ethylthiazole-2-yl, 4-(2,6-diethoxy-3-bromophenyl)thiazole-2-yl, 2-thiophene-2-ylphenyl, 2-(pyrrolidone-N-yl)phenyl, 1-phenyl-3-tert-butylpyrazole-5-yl, 4-(4-(1-ethyltetrazolone-4-yl)phenyl)thiazole-2-yl, 4-(4-diethylaminocarbonylphenyl)-5-phenylthiazole-2-yl, 4-(4-(N-pyrrolidinyl)phenyl)-5-

trifluoromethylthiazole-2-yl, 4-(4-pyrimidine-5-ylphenyl)thiazole-2-yl, 4-(4-morpholine-N-yl-3-fluorophenyl)-5-ethylthiazole-2-yl, 4-(4-morpholine-N-yl-3-fluorophenyl)-5-propylthiazole-2-yl, 4-(2-fluoropyridine-4-yl)thiazole-2-yl, 4-(2-fluoropyridine-3-yl)thiazole-2-yl, 4-(4-azacyclohept-N-yl-3-fluorophenyl)thiazole-2-yl, 4-(2-chlororopyridine-4-yl)thiazole-2-yl, 4-(2-methoxypyridine-5-yl)thiazole-2-yl, 4-(3-fluoropyridine-4-yl)thiazole-2-yl, 4-(3,4-dichlorophenyl)-5-nitrothiazole-2-yl, 4-(1-methyl-2,3-dihydroindene-6-yl)thiazole-2-yl, 4-(8-chloroquinoline-3-yl)thiazole-2-yl, 4-(4-pyrrolidine-N-yl-2,3-difluorophenyl)-5-ethylthiazole-2-yl, 4-(2-(pyrrolidine-N-yl)thiazole-4-yl)thiazole-2-yl, 4-(4,5-benzo-2,1,3-oxadiazole-5-yl)thiazole-2-yl, 4-(2-dimethylaminopyridine-5-yl)thiazole-2-yl, 4-(2-fluoropyridine-5-yl)thiazole-2-yl, 4-((4-methylpiperazine-N-yl)pyridine-6-yl)thiazole-2-yl, 4-(3-fluoro-2-methylpyridine-6-yl)thiazole-2-yl, or wherein R^1 and R^2 are both methyl, D, R^3 , R^4 and R^5 are all H, n is 2 and Ar-Cy is 3-(2-methylpyrimidine-4-yl)phenyl or wherein R^1 and R^2 are both methyl, R^3 , R^4 and R^5 are all H, D is trifluoromethyl, n is 2 and Ar-Cy is 4-(4-chlorophenyl)thiazole-2-yl.

d) Any one or more of the compounds described in WO2009/152261 A1;

e) Any one or more compounds of structure I wherein R^1 and R^2 are both methyl, D, R^3 , R^4 and R^5 are all H, n is 1 and Ar-Cy is any one of 4-phenylthiazole-2-yl, 4-(4-bromophenyl)thiazole-2-yl, 2- or 4-(N-morpholinyl)phenyl, 4-(N-piperidinyl)phenyl, 1-phenyl-3-methylpyrazole-5-yl, 4-(3,4-dimethylphenyl)thiazole-2-yl, 4-(4-ethylphenyl)thiazole-2-yl, 4-(2,4,6-trimethylphenyl)thiazole-2-yl, 4-(4-n-propylphenyl)thiazole-2-yl, 4-(4-chlorophenyl)-5-methylthiazole-2-yl, 4-phenylphenyl, 2-(N-pyrrolidinyl)phenyl, 4-(N-azacycloheptyl)phenyl, 4-phenyl-5-ethylthiazole-2-yl, 2- or 4-cyclopentylphenyl, or wherein R^2 is methyl, R^1 , D, R^3 , R^4 and R^5 are all H, n is 1 and Ar-Cy is 4-cyclopentylphenyl.

f) Any one or more of the compounds described in WO2007/073505 A1;

g) Any one or more compounds of structure I wherein R^1 and R^2 are both methyl, D, R^3 , R^4 and R^5 are all H, n is 1 and Ar-Cy is any one of 4-phenylthiazole-2-yl, 4-(4-bromophenyl)thiazole-2-yl, 2- or 4-(N-morpholinyl)phenyl, 4-(N-piperidinyl)phenyl, 1-phenyl-3-methylpyrazole-5-yl, 2-(2-benzimidazolyl)phenyl, 4-(3,4-dimethylphenyl)thiazole-2-yl, 4-(4-ethylphenyl)thiazole-2-yl, 4-(2,4,6-trimethylphenyl)thiazole-2-yl, 4-(4-n-propylphenyl)thiazole-

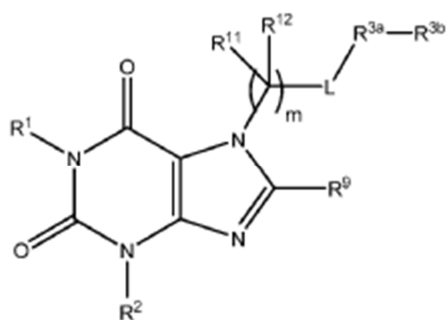
2-yl, 4-(4-chlorophenyl)-5-methylthiazole-2-yl, 4-phenylphenyl, 2-(N-pyrrolidinyl)phenyl, 4-(N-azacycloheptyl)phenyl, 4-phenyl-5-ethylthiazole-2-yl,

h) Any one or more of the compounds described in WO2009/002933 A1;

i) A compound of structure I wherein R^1 and R^2 are both methyl, D, R^3 , R^4 and R^5 are all H, n is 1 and Ar-Cy is 4-(4-diethylaminophenyl)thiazole-2-yl.

j) Any one or more of the compounds described in WO2009/140519 A1;

k) a compound of the formula shown below, or a salt thereof:



wherein, each of R^1 and R^2 is independently H, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl, each of which is optionally substituted with 1-4 R^5 ; L is NR^6SO_2 , SO_2NR^6 , $OC(O)NR^6$, $NR^6C(O)O$, $NR^6C(O)NR^6$, $NR^6C(O)$, $C(O)NR^6$, O, C(O), S, S(O), S(O)₂, NR_6 , or CH_2 , each of R^a and R is independently cyclyl, heterocyclyl, aryl, heteroaryl, each of which is optionally substituted with 1-4 R^7 ; each of R^{11} and R^{12} is, independently, H, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl, halo, hydroxyl, alkoxy, amino, alkylamino, thiol, alkylthiol, nitro, or cyano, each of which is optionally substituted with 1-2 R; each R is independently halo, hydroxyl, alkoxy, amino, alkylamino, dialkylamino, cyano, nitro, amido, alkylamido, dialkylamido, thioyl, sulfonyl, cyclyl, heterocyclyl, aryl, or heteroaryl; each R^6 is independently H, C₁-C₆ alkyl, C₁-C₆ alkenyl, hydroxyC₁-C₆ alkyl, alkoxyC₁-C₆ alkyl, cyanoalkyl, haloalkyl, arylalkyl, S(O)alkyl, acyl, amino, amidyl, or S(O)₂H, aryl, alkoxyaryl; each R^7 is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl, halo, hydroxyl, alkoxy, oxo, aryl, heteroaryl, cyclyl, heterocyclyl, arylalkyl, heteroarylalkyl, cyclylalkyl, heterocyclylalkyl, aryloxy, arylalkoxy, amino, alkylamino, dialkylamino, thioyl, alkylthioyl, sulfonyl, sulfonamidyl, amido, hydroxyl alkoxy, alkoxy -C(O)OH, -C(O)Oalkyl, urea, sulfonylurea, acyl, nitro, cyano, each of which is optionally substituted with 1-3 R; each R^8 is independently C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆

alkynyl, aryl, heteroaryl, cyclyl, halo, hydroxyl, alkoxy, oxo, aryloxy, amino, akylamino, dialkylamino, C(O)OH, -C(O)Oalkyl, thioyl, sulfonyl, sulfonamidyl, amido, urea, sulfonylurea, acyl, nitro, cyano, cyclyl, heterocyclyl, aryl, or heteroaryl; R⁹ is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl, halo, C₁-C₆ haloalkyl, hydroxyl, alkoxy, aryloxy, arylalkoxy, amino, akylamino, dialkylamino, thioyl, alkylthioyl, sulfonyl, sulfonamidyl, amido, urea, sulfonylurea, acyl, nitro, cyano, each of which is optionally substituted with 1 -3 R⁸; and m is 1, 2, 3, 4, 5, or 6.

l) Any one or more compounds of structure I wherein R¹ and R² are both methyl, D, R³, R⁴ and R⁵ are all H, n is 1 and Ar-Cy is any one of 4-(4-bromophenyl)-6-trifluoromethylpyrimidine-2-yl, 4-(3,4-dimethoxyphenyl)thiazole-2-yl, 4-(2,4-dimethylphenyl)thiazole-2-yl, 4-(2-fluorophenyl)thiazole-2-yl, 4-(3,4-difluorophenyl)-5-methylthiazole-2-yl, 4-(3,4-methylenedioxyphenyl)thiazole-2-yl, 4-(4-methoxynaphth-1-yl)thiazole-2-yl, 4-(benzo-2-piperidino)thiazole-2-yl, 4-(3-chloro-4-methoxyphenyl)thiazole-2-yl, 4-(4-ethoxyphenyl)-5-methylthiazole-2-yl, 4-(4-methylcarbonylaminophenyl)thiazole-2-yl, 4-(4-bromophenyl)-5-methylthiazole-2-yl, 4-(4-(2-methoxyethyl)phenyl)thiazole-2-yl, 4-(4-methyl-3-nitrophenyl)thiazole-2-yl, 4-(4-t-butylcarbonylaminophenyl)thiazole-2-yl, 4-phenyl-5-(1-methylimidazole-2-yl)thiazole-2-yl, 4-(4-(difluoromethoxy)phenyl)-5-methylthiazole-2-yl, 4-(2,5-diethoxyphenyl)thiazole-2-yl, 4-(4-fluorophenyl)-5-methylthiazole-2-yl, 4-phenyl-5-methylcarbonylthiazole-2-yl, 4-(3-chloro-4-fluorophenyl)thiazole-2-yl, 4-(3-fluorophenyl)thiazole-2-yl, 4-(3-methoxyphenyl)thiazole-2-yl, 4-(2-ethoxyphenyl)thiazole-2-yl, 4-(3-chlorophenyl)thiazole-2-yl, 4-(2-methoxyphenyl)thiazole-2-yl, 4-(2-bromophenyl)thiazole-2-yl, 4-(4-(dimethylamino)phenyl)thiazole-2-yl, 4-(2-chlorophenyl)thiazole-2-yl, 4-(4-methoxyphenyl)thiazole-2-yl, 4-(3-bromophenyl)thiazole-2-yl, 4-(4-methylcarbonylamino-2-fluorophenyl)thiazole-2-yl, 4-(4-isopropoxyphenyl)thiazole-2-yl, 4-(2,3,4-trichlorophenyl)thiazole-2-yl, 4-(3-chloro-4-methoxyphenyl)thiazole-2-yl, 4-(3-fluoro-4-chlorophenyl)thiazole-2-yl, 4-(3-ethoxyphenyl)thiazole-2-yl, 4-(3-nitrophenyl)thiazole-2-yl, 4-(4-phenylphenyl)thiazole-2-yl, 4-(2,4-dimethoxyphenyl)thiazole-2-yl, 4-(2,4-dimethylphenyl)thiazole-2-yl, 4-(4-cyanophenyl)thiazole-2-yl, 4-(4-ethylphenyl)thiazole-2-yl, 4-(2-methylphenyl)thiazole-2-yl, 4-(2-bromo-5-ethoxyphenyl)thiazole-2-yl, 4-(2-chloro-4-ethoxyphenyl)thiazole-2-yl, 4-(2-chloro-4-ethoxy-5-bromophenyl)thiazole-2-yl, 4-(2-pyridyl)thiazole-2-yl, 4-(4-(2-hydroxyethoxy)phenyl)thiazole-2-yl, 4-(3-(2-hydroxyethoxy)phenyl)thiazole-2-yl, 4-(2,6-dichlorophenyl)thiazole-2-yl, 4-(3-methylphenyl)thiazole-2-yl, 4,5-bis(4-methylphenyl)oxazole-2-yl, 4,5-diphenyloxazole-2-yl, 4-

(4-pyridyl)thiazole-2-yl, 4-(2-(2-hydroxyethoxy)phenyl)thiazole-2-yl, 4-(3,4-dichlorophenyl)-5-methylthiazole-2-yl, 4-(2,4,6-trichlorophenyl)thiazole-2-yl, 4-(4-ethoxyphenyl)-5-phenylthiazole-2-yl, 4-(4-chloro-3-ethoxyphenyl)thiazole-2-yl, 4-(3,4,5-trichlorophenyl)thiazole-2-yl, 2-(4-pyridyl)1,3,4-thiadiazole-5-yl, 4-(2-(2-hydroxyethoxy)-5-bromophenyl)thiazole-2-yl, 3-(benzoxazole-2-yl)-2-methylphenyl, 4-(2,3-dichlorophenyl)-5-ethylthiazole-2-yl, 4-(3-trifluoromethylphenyl)thiazole-2-yl, 4-(3,4-dichlorophenyl)-5-phenylthiazole-2-yl, 4-(3,4-dichlorophenyl)-5-(4-methylphenyl)thiazole-2-yl, 1-phenyl-3-(4-methylphenyl)pyrazole-5-yl, 3-(4-fluorophenyl)pyrazole-5-yl, 4,5-bis(3,4-dichlorophenyl)thiazole-2-yl, 5-phenylthiazole-2-yl, 5-(4-chlorophenyl)thiazole-2-yl, 4-(4-trifluoromethylphenyl)thiazole-2-yl, 4-(4-methylsulfonylphenyl)thiazole-2-yl, 4,5-bis(2-furyl)thiazole-2-yl, 4-(4-chlorophenyl)oxazole-2-yl, 4-(4-trifluoromethoxyphenyl)thiazole-2-yl, 3-(4-chlorophenyl)pyrazole-2-yl, 2-(4-chlorophenyl)-1,3,4-oxadiazole-5-yl, 3-phenylpyrazole-5-yl, 5-(4-methylphenyl)thiazole-2-yl, 4-(4-chlorophenyl)-5-ethylthiazole-2-yl, 4-(4-nitrophenyl)thiazole-2-yl, 4-(4-aminophenyl)thiazole-2-yl, 4-(4-ethoxylphenyl)-5-methylthiazole-2-yl, 4-(4-diethylamino-3-fluorophenyl)thiazole-2-yl, 3-(thiophene-2-yl)pyrazole-5-yl, 4-(4-chlorophenyl)-5-fluorothiazole-2-yl, 4-(4-chlorophenyl)-5-aminothiazole-2-yl, 2-(pyrrole-N-yl)phenyl, 2-(indole-2-yl)phenyl, 4-(benzimidazoloneyl)thiazole-2-yl, 2-chlorophenylpyrid-4-yl, 3-(4-chlorophenyl)phenyl, 4-(4-diethylamino-3-chlorophenyl)thiazole-2-yl, 5-(4-ethoxyphenyl)thiazole-2-yl, 3-(4-chlorophenyl)-5-pyridyl, 4-(3,4-dichlorophenyl)-5-isopropylthiazole-2-yl, 4-(4-diethylamino-2-fluorophenyl)thiazole-2-yl, 4-(4-(N-pyrrolidinyl)-3-bromophenyl)thiazole-2-yl, 4-(4-fluoro-3-N-morpholinylphenyl)thiazole-2-yl, 2-(4-chlorophenyl)pyrazine-6-yl, 4-(2,4,5-trichlorophenyl)thiazole-2-yl, 5-(4-diethylaminophenyl)thiazole-2-yl, 4-(1-ethoxynaphth-4-yl)thiazole-2-yl, 4-(2,3-dihydrobenzofuran-5-yl)thiazole-2-yl, 2-(3,4-dichlorophenyl)thiazole-4-yl, 4-phenyl-5-(4-ethoxyphenyl)imidazole-2-yl, 4-(4-(N-piperidinyl)phenyl)thiazole-2-yl, 4-(3-diethylaminophenyl)thiazole-2-yl, 2-(benzothiazole-2-yl)phenyl, 4-(3-(N-piperidinyl)phenyl)thiazole-2-yl, 4-(3-dimethylaminophenyl)thiazole-2-yl, 4-(4-chlorophenyl)pyridine-2-yl, 3-(4-diethylaminophenyl)phenyl, 4-(4-ethoxyphenyl)pyrazole-2-yl, 4-(4-ethoxyphenyl)-5-methylpyrazole-2-yl, 4-(N-acetyl-2,3-dihydroindole-5-yl)thiazole-2-yl, 4-(3,4-dichlorophenyl)pyrimidine-2-yl, 3-(thiazole-2-yl)phenyl, 4-(quinoline-2-yl)thiazole-2-yl, 4-(4-diethylamino-3,5-difluorophenyl)thiazole-2-yl, 4-(3-(N-pyrrolidinyl)phenyl)thiazole-2-yl, 4-(4-aminocarbonylaminophenyl)thiazole-2-yl, 4-(4-chlorophenyl)-5-methoxylthiazole-2-yl, 4-(4-(diethylaminosulfonyl)phenyl)thiazole-2-yl, 4-(4-(dimethylaminosulfonyl)phenyl)thiazole-2-yl, 4-(dihydrobenzoxazine-3-one-6-yl)thiazole-2-yl, 4-(3,4-dichlorophenyl)imidazole-2-yl, 4-

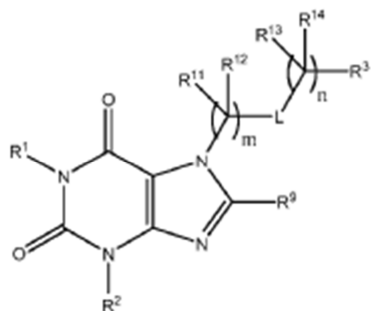
(4-ethoxyphenyl)oxazole-2-yl, 4-(4-chlorophenyl)oxazole-2-yl, 3-(4-ethylthiazole-2-yl)phenyl, 3-(5-ethylthiazole-2-yl)phenyl, 3-(4-methylthiazole-2-yl)phenyl, 4-(4-diethylamino-2-chlorophenyl)thiazole-2-yl, 4-(4-diethylamino-2, 5-difluorophenyl)thiazole-2-yl, 4-(3-trifluoromethoxyphenyl)thiazole-2-yl, 2-(4-chlorophenyl)pyrid-6-yl, 3-(4-diethylamino-3-fluorophenyl)phenyl, 4-(4-diethylamino-2,3-difluorophenyl)thiazole-2-yl, 4-(4-(N-piperidinylsulfonyl)phenyl)thiazole-2-yl, 4-(N-acetylindole-5-yl)thiazole-2-yl, 4-(2-ethoxynaphth-1-yl)thiazole-2-yl, 1-(phenylmethyl)-4-(3,4-diphenyl)imidazole-2-yl, 4-(N-ethyl-2,3-dihydroindole-5-yl)thiazole-2-yl, 3-(4-chlorophenyl)1,2,4-thiadiazole-5-yl, 4-(N-acetyl-2,3-dihydroindole-6-yl)thiazole-2-yl, 4-(N-ethylindole-5-yl)thiazole-2-yl, 3-(4-chlorophenyl)thiophene-5-yl, 1-(4-chlorophenyl)1,2,4-triazole-3-yl, 1-phenylpyrazole-4-yl, 4-(N-acetylindole-6-yl)thiazole-2-yl, 4-N-methyl-2,3-dihydroindole-5-yl)thiazole-2-yl, 4-(4-diethylamino-2-chloro-5-fluorophenyl)thiazole-2-yl, 4-(3-dimethylaminosulfonylphenyl)thiazole-2-yl, 4-(3-methylsulfonylaminophenyl)thiazole-2-yl, 4-(3-diethylaminosulfonylphenyl)thiazole-2-yl, 2-(4-chlorophenyl-1,3,5-triazine-4-yl, 4-(4-(morpholin-N-ylsulfonyl)phenyl)thiazole-2-yl), 4-(4-(N-pyrrolidinosulfonyl)phenylthiazole-2-yl), 4-(4-chloro-3-diethylaminophenyl)thiazole-2-yl, 4-(4-chloro-3-trifluoromethylphenyl)thiazole-2-yl, 1-ethyl-4-(2,3-dichlorophenyl)imidazole-2-yl, 1-methyl-4-(2,3-dichlorophenyl)imidazole-2-yl, 2-(1-naphthyl)5-pyridyl, 2-(3,4-dichlorophenyl)5-pyridyl, 4-(4-chlorophenyl)-5-dimethylaminomethylthiazole-2-yl, 4-(3-diethylaminophenyl)-5-methylthiazole-2-yl, 4-(4-diethylamino-3-fluorophenyl)-5-ethylthiazole-2-yl, 4-(4-chlorophenyl)-5-(2-dimethylaminoethyl)thiazole-2-yl, 4-(4-trifluoromethyl-2-fluorophenyl)thiazole-2-yl, 4-(3-trifluoromethyl-5-fluorophenyl)thiazole-2-yl, 4-(4-trifluoromethyl-3-fluorophenyl)thiazole-2-yl, 4-(3-trifluoromethyl-4-fluorophenyl)thiazole-2-yl, 4-(3,4-dichlorophenyl)-5-methoxycarbonylthiazole-2-yl, 4-(1-bromo-2-ethoxynaphth-6-yl)thiazole-2-yl, 4-(3,4-dichlorophenyl)-5-methoxycarbonylmethylthiazole-2-yl, 1,5-dimethyl-4-(3,4-dichlorophenyl)imidazole-2-yl, N-(4-chlorophenyl)pyrrole-3-yl, 4-(3,4-dichlorophenyl)-5-aminocarbonylthiazole-2-yl, 4-(2-ethoxynaphth-6-yl)thiazole-2-yl, 4-(3,4-dichlorophenyl)-5-hydroxycarbonylmethylthiazole-2-yl, 4-(4-diethylamino-2,5-difluorophenyl)-5-ethylthiazole-2-yl, 4-(4-(N-pyrrolidinyl)-3-fluorophenyl)thiazole-2-yl, 4-(4-diethylamino-3-ethoxyphenyl)thiazole-2-yl, 4-(4-diethylamino-2-ethoxyphenyl)thiazole-2-yl, 4-(4-(N-pyrrolidinyl)-3-(trifluoromethyl)phenyl)thiazole-2-yl, 4-(4-diethylamino-3-trifluoromethylphenyl)thiazole-2-yl, 4-(1-n-butyl-4-(3,4-dichlorophenyl)imidazole-2-yl, 1-(4-chlorophenyl)imidazole-4-yl, 4-(2-indolyl)thiazole-2-yl, 5-(4-chlorophenyl)isoxazole-2-yl, 5-(4-chlorophenyl)1,2,4-oxadiazole-3-yl, 1-ethyl-5-methyl-4-(3,4-dichlorophenyl)imidazole-2-yl, 4-

phenyl-5-(4-ethoxyphenyl)oxazole-2-yl, 2-naphthyl-5-pyridyl, 2-(4-chlorophenyl)oxazole-5-yl, 4-(3-methylethylaminophenyl)-5-ethylthiazole-2-yl, 4-(4-ethoxyl-3-diethylaminophenyl)thiazole-2-yl, 4-(4-diethylaminophenyl)-5-fluorothiazole-2-yl, 4-(4-(4-ethylpiperazine-1-yl)-3-trifluoromethylphenyl)thiazole-2-yl, 4-(3-ethoxycarbonylphenyl)thiazole-2-yl, 4-(4-(N-pyrrolidinyl)-3,4-difluorophenyl)thiazole-2-yl, 4-(4-chlorophenyl)-5-trifluoromethylthiazole-2-yl, 4-(4-diethylamino-3-cyanophenyl)thiazole-2-yl, 4-(2-ethoxynaphth-5-yl)thiazole-2-yl, 4-(4-chlorophenyl)isothiazole-3-yl, 4-(N-methylindole-5-yl)thiazole-2-yl, 4-(3,4-dichlorophenyl)-5-(2-hydroxyethyl)thiazole-2-yl, 4-(4-chlorophenyl)thiazole-2-yl in which case D is trifluoromethyl, 1-(4-chlorophenyl)1,2,3-triazole-4-yl, 4-(4-(2*H*-imidazole-1-yl)phenyl)thiazole-2-yl, 4-(4-tetrazole-5-ylphenyl)thiazole-2-yl, 4-(4-methyl-4-methoxyphenylmethylaminophenyl)thiazole-2-yl, 4-(4-(N-pyrrolidinyl)-3,5-difluorophenyl)-5-fluorothiazole-2-yl, 4-(4-N-morpholinyl-3-trifluoromethylphenyl)thiazole-2-yl, 4-(4-(N-piperidinyl)-3-(trifluoromethyl)phenyl)thiazole-2-yl, 4-(4-nitrophenyl)-5-trifluoromethylthiazole-2-yl, 4-(4-diethylamino-3-trifluoromethylphenyl)-5-trifluoromethylthiazole-2-yl, 4-(3-hydroxycarbonylphenyl)thiazole-2-yl, 4-(4-hydroxycarbonylphenyl)thiazole-2-yl, 4-(4-N-pyrrolidinyl-2,5-difluorophenyl)thiazole-2-yl, 4-(4-diethylamino-3-fluorophenyl)-5-fluorothiazole-2-yl, 4-(4-diethylamino-3-trifluoromethylphenyl)-5-trifluoromethylthiazole-2-yl, 4-(4-aminophenyl)-5-trifluoromethylthiazole-2-yl, 4-(4-(N-pyrrolidinyl)phenyl)thiazole-2-yl, 4-(4-(4-ethylpiperazine-1-yl)phenyl-2,5-difluorophenyl)thiazole-2-yl, 4-(4-diethylaminophenyl)-5-trifluoromethylthiazole-2-yl, 4-(4-diethylamino-3,5-difluorophenyl)-5-fluorothiazole-2-yl, 4-(4-(N-morpholinyl)-2,5-difluorophenyl)thiazole-2-yl, 4-(4-(N-piperidinyl)-2,5-difluorophenyl)thiazole-2-yl, 4-(4-(N-pyrazolyl)-3-fluorophenyl)thiazole-2-yl, 4-(4-chlorophenyl)-5-methylthiazole-2-yl, 3-(5-methylthiazole-2-yl)phenyl, 4-(1-ethoxynaphth-3-yl)thiazole-2-yl, 5-(4-chlorophenyl)isothiazole-3-yl, 4-(5-benzofuryl)thiazole-2-yl, 3-(4-chlorophenyl)isoxazole-5-yl, 4-(3-N-pyrrolidinylcarbonylphenyl)thiazole-2-yl, 4-(4-diethylaminophenyl)-5-phenylthiazole-2-yl, 4-(3-N-morpholinylcarbonylphenyl)thiazole-2-yl, 4-(4-diethylaminophenyl)-5-trifluoromethylcarbonylthiazole-2-yl, 4-(4-diethylamino-3-fluorophenyl)-5-trifluoromethylthiazole-2-yl, 4-(4-ethylamino-3-fluorophenyl)-5-trifluoromethylthiazole-2-yl, 4-(4-diethylamino-3-fluoro-5-trifluoromethylphenyl)-5-trifluoromethylthiazole-2-yl, 4-(4-(2-dimethylaminoethoxy)-3-fluorophenyl)thiazole-2-yl, 4-(4-(N-pyrrolidinyl)phenyl)-5-ethylthiazole-2-yl, 2-(4-(N-pyrrolidinyl)-3-fluorophenyl)pyridin-5-yl, 4-(4-fluoro-3-(N-pyrrolidinyl)phenyl)thiazole-2-yl, 4-(4-diethylamino-3-(N-pyrrolidinyl)phenyl)thiazole-2-yl, 4-(4-(N-pyrrolyl)phenyl)-5-(trifluoromethyl)thiazole-2-yl, 2-

(4-chlorophenyl)thiophene-5-yl, 4-(1-ethoxynaphth-5-yl)thiazole-2-yl, 1-(4-chlorophenyl)pyrazole-3-yl, 4-(4-(N-pyrrolidinyl)-2,5-difluorophenyl)-5-ethylthiazole-2-yl, 4-(4-(N-pyrrolidinyl)-3-trifluoromethylphenyl)-5-methylthiazole-2-yl, 4-(4-(N-piperidinyl)-3-trifluoromethylphenyl)-5-methylthiazole-2-yl, 4-(4-chlorophenyl)-5-n-propylthiazole-2-yl, 4-(4-ethoxyl-2-(N-pyrrolidinyl)phenyl)thiazole-2-yl, 4-(4-chloro-2-(N-pyrrolidinyl)phenyl)thiazole-2-yl, 4-(4-(N-pyrrolidinyl)phenyl)-5-fluorothiazole-2-yl, 4-(2-chloropyridine-5-yl)thiazole-2-yl, 2-(4-(N-pyrrolidinyl)phenyl)pyridine-5-yl, 4-(4-(N-pyrrolidinyl)-3-fluorophenyl)-5-ethylthiazole-2-yl, 4-(2-chloropyridine-3-yl)thiazole-2-yl, 4-(4-(2-methylpyrrolidine-1-yl)-3-fluorophenyl)thiazole-2-yl, 4-(4-(N-pyrrolidinyl)-3-(trifluoromethyl)phenyl)-5-n-propylthiazole-2-yl, 4-(4-diethylamino-2-chlorophenyl)-5-ethylthiazole-2-yl, 4-ethyl-5-(4-chlorophenyl)thiazole-2-yl, 4-(3,4-dichlorophenyl)-5-aminothiazole-2-yl, 4-(6-chloroquinoline-3-yl)thiazole-2-yl, 4-(2,4-bis(N-pyrrolidinyl)phenyl)thiazole-2-yl, 4-(4-(2,5-dimethylpyrrolidine-1-yl)-3-fluorophenyl)thiazole-2-yl, 4-benzothiophene-3-ylthiazole-2-yl, 4-(4-diethylaminophenyl)-5-ethylthiazole-2-yl, 4-(4-methylaminophenyl)thiazole-2-yl, 4-(2,6-diethoxy-3-bromophenyl)thiazole-2-yl, 2-(thiophene-2-yl)phenyl, 2-(pyrrolidone-N-yl)phenyl, 1-phenyl-3-t-butylpyrazole-5-yl, 4-(4-(1-ethyltetrazolone-4-yl)phenyl)thiazole-2-yl, 4-(4-diethylaminocarbonylphenyl)-5-phenylthiazole-2-yl, 4-(4-(N-pyrrolyl)phenyl)-5-(trifluoromethyl)thiazole-2-yl, 4-(pyrimidine-5-yl)thiazole-2-yl, 4-(4-(N-morpholinyl)-3-fluorophenyl)-5-n-propylthiazole-2-yl, 4-(2-fluoropyrine-4-yl)thiazole-2-yl, 4-(2-fluoropyrine-3-yl)thiazole-2-yl, 4-(4-(N-azacycloheptyl)-3-fluorophenyl)thiazole-2-yl, 4-(2-chloropyridine-4-yl)thiazole-2-yl, 4-(2-methoxypyridine-5-yl)thiazole-2-yl, 4-(3-fluoropyrine-4-yl)thiazole-2-yl, 4-(3,4-dichlorophenyl)-5-nitrothiazole-2-yl, 4-(N-methyl-2,3-dihydroindole-6-yl)thiazole-2-yl, 4-(8-chloroquinoline-3-yl)thiazole-2-yl, 4-(4-(N-pyrrolidinyl)-2,3-difluorophenyl)-5-ethylthiazole-2-yl, 4-(2-(N-pyrrolidinyl)thiazole-4-yl)thiazole-2-yl, 4-(benzofurazan-4-yl)thiazole-2-yl, 4-(2-dimethylaminopyridine-5-yl)thiazole-2-yl, 4-(2-fluoropyridine-5-yl)thiazole-2-yl, 4-(2-(4-methylpiperidine-1-yl)pyridine-6-yl)thiazole-2-yl, 4-(3-fluoro-2-methylpyridine-6-yl)thiazole-2-yl.

m) Any one or more of the compounds described in WO2009/140517 A1;

n) a compound of the formula below or a salt thereof,



wherein each of R^1 and R^2 is, independently, H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, or C_2 - C_6 alkynyl, each of which is optionally substituted with 1-4 R^5 ; L is NR^6SO_2 , SO_2NR^6 , $C(O)NR^6$, $NR^6C(O)$, $OC(O)NR^6$, $NR^6C(O)O$, $NR^6C(O)NR^6$, S, $S(O)$, $S(O)_2$, NR^6 , CH_2 , O, $C(O)NS(O)_2$, $S(O)_2NC(O)$, heteroaryl, or cyclyl; R is C_4 - C_{14} cyclyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with 1-4 R^7 ; each R^5 is independently halo, hydroxyl, alkoxy, thiol, alkylthio, amino, alkylamino, dialkylamino, cyano, nitro, amido, alkylamido, dialkylamido, thioyl, sulfonyl, cyclyl, heterocyclyl, aryl, or heteroaryl; each R^6 is independently H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, aryl, arylalkyl, or acetyl; each R^7 is independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cyclyl, heterocyclyl, aryl, heteroaryl, halo, hydroxyl, alkoxy, thiol, alkylthio, aryloxy, arylalkoxy, amino, alkylamino, dialkylamino, thioyl, alkylthioyl, sulfonyl, sulfonamidyl, amido, urea, sulfonylurea, hydroxyl alkoxyl, alkoxy alkoxyl, acyl, nitro, or cyano, each of which is optionally substituted with 1-3 R^8 ; each R^8 is independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, or C_2 - C_6 alkynyl, halo, hydroxyl, alkoxy, thiol, alkylthio, aryloxy, amino, alkylamino, dialkylamino, thioyl, sulfonyl, sulfonamidyl, amido, urea, sulfonylurea acyl, nitro, cyano, cyclyl, heterocyclyl, aryl, or heteroaryl; R^9 is independently H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, or C_2 - C_6 alkynyl, halo, hydroxyl, alkoxy, aryloxy, arylalkoxy, amino, alkylamino, dialkylamino, thioyl, alkylthioyl, sulfonyl, sulfonamidyl, amido, urea, sulfonylurea, acyl, nitro, cyano, and is optionally substituted with 1-3 R^8 ; each of R^{11} - R^{14} is, independently, H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, or C_2 - C_6 alkynyl, halo, hydroxyl, alkoxy, amino, alkylamino, thiol, alkylthiol, nitro, or cyano, each of which is optionally substituted with 1-2 R^8 ; each of m and n is, independently, 0, 1, 2, 3, 4, 5, or 6.

o) Any one or more, optionally all, of the compounds 7, 13, 17, 27, 28, 39, 42, 43, 44, 58, 65, 71 and 80, and also optionally 83, described hereinafter.

[00013] The following particular options may be used in conjunction with the first aspect, either individually or in any suitable combination.

[00014] R^1 and R^2 may, independently, be methyl or ethyl. They may both be methyl. R^3 and R^4 may both be H. They may both be alkyl, e.g. methyl or ethyl. One of R^3 and R^4 may be alkyl (e.g. methyl or ethyl) and the other H. R^5 may be hydrogen. It may be methyl or may be some other alkyl.

[00015] If Ar is a 6-membered ring, it may be 1,4-disubstituted. If Ar is a 5-membered ring it may be 1,3-disubstituted. Ar may be a ring which is not 1,2-disubstituted. In this context, “disubstituted” refers to substitution by Cy and NR^5 .

[00016] Ar may be a disubstituted benzene ring (i.e. a phenylene ring), a disubstituted thiophene ring or a disubstituted nitrogen heterocycle having between 1 and 4 nitrogen atoms. It may be a 6 membered aromatic ring having between 0 and 2 nitrogen atoms. It may be a ring that is not a 2-thiazolyl ring. It may be a pyridazine ring, e.g. a pyridazin-3,6-diyl.

[00017] Cy may be a 5 or 6 membered aromatic ring having between 0 and 2 nitrogen atoms, 0 or 1 sulfur atoms and 0 or 1 oxygen atoms. Alternatively it may be piperazine. The piperazine may be substituted on both nitrogen atoms. Cy may contain no chlorine. It may be a group that is not a chlorophenyl group (optionally additionally substituted). In some embodiments compound I has no chlorine.

[00018] n may be 1.

[00019] D may be H.

[00020] The modulating may be inhibiting.

[00021] In a particular embodiment, R^1 and R^2 are both methyl, R^3 , R^4 , R^5 and D are all H and n is 1. In a specific instance of this embodiment, Ar is a 6-membered ring having 1 or 2 nitrogen atoms and having no substituents other than Cy and the amide nitrogen, these being in a 1,4-relationship on the ring.

[00022] The compound may have an IC_{50} against STF3A of less than 10 micromolar, or less than 5 micromolar or less than 1 micromolar, or less than 0.1 micromolar.

[00023] The compound may not modulate, or may not inhibit, TRPA1. It may not inhibit TRPA1 at an IC_{50} of < 5 micromolar or at an IC_{50} of < 10 micromolar.

[00024] The above embodiment also includes all enantiomers and diastereomers of the compound, as well as salts of the compounds. Suitable salts include pharmaceutically and/or veterinarily acceptable salts, for example the hydrochloride salts. The free bases of the compounds are also encompassed.

[00025] In an embodiment, there is provided use of a compound as defined above for modulating, optionally inhibiting, Wnt activity and/or porcupine activity. There is also provided a method of modulating, optionally inhibiting, Wnt activity (e.g. Wnt secretion) and/or porcupine activity comprising exposing cells, or a Wnt protein or a Wnt receptor, to a compound as defined above. The cells may be cells that over-express Wnt protein. The method may be an *in vitro* method or it may be an *in vivo* method. Without wishing to be bound by theory, the inventors hypothesise that the compounds defined above inhibit the secretion of Wnt proteins. The compounds as defined above are capable of inhibiting porcupine, which is essential and specific for the palmitoylation of Wnt proteins before secretion. Thus in an embodiment there is provided a method of inhibiting, Wnt secretion in a cell, said method comprising exposing said cell to a compound as defined above. In another embodiment there is provided a method of inhibiting Wnt secretion in a cell which over-expresses Wnt protein, said method comprising exposing said cell to a compound as defined above.

[00026] In another embodiment, there is provided use of a compound as defined above for treatment of a disease or condition associated with Wnt pathway activity. The Wnt pathway activity may be excessive activity. This embodiment also includes a method for treating said disease or condition, comprising administering to a subject in need thereof a therapeutically effective amount of the compound. The subject may be a human or may be a non-human, e.g. a non-human mammal or other non-human animal.

[00027] The disease or condition may be selected from the group consisting of cancer, fibrosis, stem cell and diabetic retinopathy. The cancer may be a cancer characterised by abnormal, optionally high, Wnt activity.

[00028] In another embodiment there is provided use of a compound as defined above for the manufacture of a medicament for the treatment of a disease or condition associated with abnormal, optionally high, Wnt pathway activity. The disease or condition may be selected from the group consisting of cancer, fibrosis, stem cell and diabetic retinopathy, rheumatoid arthritis, psoriasis and myocardial infarction. There is also provided a composition or medicament for the treatment of such a disease or condition, said composition or medicament comprising a compound as defined above together with one or more pharmaceutically acceptable carriers, diluents or adjuvants.

[00029] The disease or condition may be a cancer, such as cervical, colon, breast, bladder, head and neck, gastric, lung, ovarian, prostate, thyroid, non-small-cell lung, as well as chronic lymphocytic leukemia, mesothelioma, melanoma, pancreatic adenocarcinoma, basal cell carcinoma, osteosarcoma, hepatocellular carcinoma, Wilm's tumour or medulloblastoma. The disease or condition may be a severe fibrotic disease, such as pulmonary fibrosis, liver fibrosis, skin fibrosis or renal fibrosis. It may be a degenerative disease. It may be a metabolic disease such as diabetic retinopathy.

[00029a] In another aspect, there is provided the use of a compound as defined above in the manufacture of a medicament for the treatment of a disease or condition associated with Wnt pathway activity, said disease or condition being selected from the group consisting of cancer, such as cervical, colon, breast, bladder, head and neck, gastric, lung, ovarian, prostate, thyroid, non-small-cell lung, as well as chronic lymphocytic leukemia, mesothelioma, melanoma, pancreatic adenocarcinoma, basal cell carcinoma, osteosarcoma, hepatocellular carcinoma, Wilm's tumor or medulloblastoma, or a fibrotic disease, such as pulmonary fibrosis, liver fibrosis, skin fibrosis or renal fibrosis, or a degenerative disease, or a metabolic disease such as diabetic retinopathy.

[00030] In an embodiment, there is provided a compound as defined above for use in therapy.

[0030a] In another aspect, there is provided the use of a compound as defined above in diagnosis.

[00031] In another aspect, there is provided a pharmaceutical composition comprising a compound as defined above together with one or more pharmaceutically acceptable carriers, diluents or adjuvants.

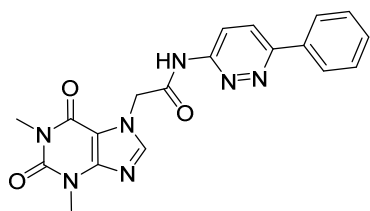
[00032] In another aspect, there is provided an anhydrous form of the free base of 2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)-N-(6-phenylpyridazin-3-yl)acetamide. There is also provided a pharmaceutical composition comprising said anhydrous free base, a method of treating or preventing a proliferative disorder comprising administering a therapeutically effective amount of said anhydrous free base to a subject in need thereof and use of said anhydrous free base either in the treatment of a proliferative disorder or in the manufacture of a medicament for the treatment of a proliferative disorder.

[00032a] In another aspect, there is provided a pharmaceutical composition comprising an anhydrous free base as defined above.

[00032b] In another aspect, there is provided a use of an anhydrous free base as defined above in the manufacture of a medicament for the treatment of a proliferative disorder regulated by the Wnt pathway.

Brief Description of Drawings

[00033] Figure 1 shows tumour weights and volumes in mice treated with Compound 5:



[00034] Figure 2 shows images of tumours treated with Compound 5.

[00035] Figure 3 shows the time-course of p-LRP6 (Ser 1490) inhibition (*in vitro*) induced by porcupine inhibitors. It is a Western blot analysis of PA-1 teratocarcinoma cells treated with 2 μ M of Compound 5, for the time points indicated. As a control, cells treated with either growth medium alone or the vehicle (DMSO) for 48 h were included. (A) Western blots with antibodies as indicated on the left. (B) Densitometric analysis of pLRP6 relative to total LRP6.

[00036] Fig. 4 shows pLRP6 *in vitro* inhibition-dose titration. It is a Western blot analysis of HPAF-II pancreatic adenocarcinoma cells treated with the indicated doses of Compound 5 for 6 h. The positive controls are a cell lysate of untreated STF3A cells and cells treated with vehicle only (DMSO). (A) Western blots with antibodies as indicated on the left. (B) Densitometric analysis of pLRP6 relative to total LRP6.

Description of Embodiments

[00037] The invention relates to the preparation and the use of new compounds that modulate Wnt activity, to methods of using the compounds, as a single agent or in combination, for treating or preventing diseases and conditions associated with Wnt pathway activity, in particular having a dysfunction linked to Wnt signalling pathway i.e. cancer, fibrosis, stem cell and diabetic retinopathy. Thus the invention relates to a class of compounds that act as modulators of the Wnt pathway and to pharmaceutical compositions comprising these compounds and to their use for the preparation of a medicament for the treatment of diseases having a dysfunction linked to Wnt signalling pathway where Wnt plays a role in proliferation of cancer via multiple mechanisms, including a key role in stem cell maintenance. Dysfunction of the Wnt pathway is related to conditions including, but not limited to, cancers such as cervical, colon, breast, bladder, head and neck, gastric, lung, ovarian, prostate, thyroid, non-small-cell lung, as well as chronic lymphocytic leukemia, mesothelioma, melanoma, pancreatic

adenocarcinoma, basal cell carcinoma, osteosarcoma, hepatocellular carcinoma, Wilm's tumour and medulloblastoma and other diseases with high Wnt expression such as fibrosis (including skin, idiopathic pulmonary, liver, renal interstitial, myocardial, infarct and liver) and diabetic retinopathy. Respiratory conditions, or respiratory tumours, may in certain embodiments not be conditions treated by the present invention.

[00038] Many of the compounds of the present invention are 1,3-dimethyl-3,7-dihydro-1H-purine-2,6-diones or 1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurines and related compounds. The general structure of these is structure (I) as defined earlier. In this definition the following may apply.

[00039] Alkyl groups may be linear or may be branched. They may be C1 to C12 or may be more than C12. They may for example be C1 to C6, C1 to C3, C3 to C6 or C6 to C12, e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, neopentyl, hexyl, octyl, isooctyl, decyl or dodecyl. In certain instances they may contain cyclic structures. Thus they may for example be, or may contain, cyclohexyl, methylcyclohexyl, isopropylcyclopentyl, cyclobutylethyl etc. In certain embodiments they are not cage structures such as adamantyl.

[00040] Aryl groups may be homoaromatic. They may be benzenoid. They may be monocyclic, bicyclic or polycyclic (i.e. contain more than 2 rings). They may comprise fused and/or unfused rings. They may, unless otherwise specified, have any suitable substitution pattern, e.g. ortho, meta, para. Unless specified, they may have any appropriate number of substituents (e.g. a monocyclic aromatic may have from 1 to 5 substituents, a fused bicyclic aromatic may have from 1 to 7 substituents etc.).

[00041] Heteroaryl groups may have 1 heteroatom, or may have 2, 3 or 4 heteroatoms or in some cases more than 4. The heteroatom(s) are commonly selected (independently) from N, S and O, however in some instances other heteroatoms may be present. Heteroaryl groups typically have 5 or 6 ring atoms unless they are bicyclic or polycyclic. Unless otherwise specified, they may have any suitable substitution pattern and may have any appropriate number of substituents. Heteroaryl groups may be monocyclic or bicyclic or polycyclic. The fused rings may each be either a heteroaryl ring or a homoaryl ring, provided that at least one is heteroaryl.

[00042] Non-aromatic rings may, unless otherwise specified, be carbocyclic or may contain one or more heteroatoms, e.g. 1, 2, 3 or 4 heteroatoms. Each heteroatom may, independently, be N,

S or O, or some other heteroatom. The rings may have from 4 to 8 ring atoms, commonly 5 or 6. Suitable examples include piperazinyl and morpholinyl rings. Group Cy in structure (I) may be, in some embodiments, an example of such rings.

[00043] The term “optionally substituted” signifies that one or more substituents may be present or there may be no substituents. Substituents may or may not be present on the above groups (alkyl, aryl, heteroaryl, non-aromatic rings). There may be 0, 1, 2, 3 or 4 or more than 4 substituents on a group, as dictated by the structure of the group. Possible substituents include halogens (e.g. fluorine, chlorine or bromine), alkyl groups, alkoxy groups (i.e. O-alkyl, where alkyl is as defined above), aryloxy groups (i.e. O-aryl, where aryl is as defined above), ester, amide or sulfonate ester groups (i.e. CO₂R, CONHR, SO₃R, where R is alkyl as defined above), however other substituents may additionally or alternatively be present. In cases where substituents are shown, the term “optionally substituted” indicates the possibility of additional substituents that are not shown. Thus for example in structure I, when it is stated that Ar is “optionally substituted”, this indicates the possibility of further substituents additional to Cy and NR⁵, but does not indicate the possibility that either Cy or NR⁵ might be absent. Thus, for example, in cases where it is stated that Ar is a “disubstituted” aromatic ring, this should be taken to mean that there are only two substituents on the ring, i.e. no additional substituents other than Cy and the amide nitrogen. For example, the 1,4-phenylene group in compound 1 is regarded as “disubstituted”.

[00044] In structures (I) and (II), n may be 1 to 5. It may be 1 to 3. It may be any one of 1, 2, 3, 4 or 5. Substituent D may be H, halogen, alkyl, cycloalkyl, aryl, or dialkylamino, each (other than H and halogen) being optionally substituted. Examples include hydrogen, chlorine, bromine, methyl, ethyl, propyl, cyclopropyl, phenyl, trifluoromethyl, dimethylamino, N-piperidinyl, N-piperazinyl, N-methyl-N'-piperazinyl etc. In many embodiments, n is 1.

[00045] In some cases, the substituents R³ and R⁴ are the same, and in others they are different. In the event that they are different, they give rise to stereochemistry at the carbon atom to which they are attached. In general the stereochemistry at that carbon (or at each carbon) may be (S) or (R). In the particular example where n is 1 and one of R³ and R⁴ is H and the other is an alkyl group, a preferred stereochemistry is as shown in structure (II), where Me represents the alkyl group. In cases where the alkyl group is methyl, this stereochemistry is particularly preferred.

[00046] Examples of group Ar in structure (I) include 1,4-phenylene, 2,5-pyridinediyl, 3,6-pyridazinediyl, 2,5-pyrazinediyl, 2,5-thiophenediyl, 2,4-thiophenediyl, 2,5-furandiyl, 2,4-furandiyl, etc. Examples of group Cy in structure (I) include phenyl, thiazole-2-yl, thiophene-2-yl, thiophene-3-yl, pyridine-1-yl, pyridine-2-yl, pyridine-3-yl, pyridazine-3-yl, pyridazine-4-yl, pyrimidine-2-yl, pyrimidine-4-yl, pyrimidine-4-yl, N-imidazolyl, 2-, 4- or 5-thiazolyl, 2-, 4- or 5-oxazolyl, N-morpholinyl or N' substituted N-piperazinyl. Suitable substituents on the N' position of the piperazinyl substituent include $-C(=O)X$, where X is t-butoxy, neopentyl, methyl, phenyl, p-chlorophenyl, benzyl, α,α -difluorobenzyl, chlorobenzyl, fluorobenzyl etc.

[00047] In some embodiments, R^1 and R^2 are the same. They may be both methyl. They may be both ethyl. In the latter case, Ar may be 1,4-phenylene and Cy may be thiophene-3-yl.

[00048] In some embodiments D is H. In other embodiments, D is methyl, cyclopropyl, trifluoromethyl, phenyl, dimethylamino, morpholin-N-yl, thiophene-3-yl or bromo. In the event that D is not H (e.g. is methyl, cyclopropyl, trifluoromethyl, phenyl, dimethylamino, morpholin-N-yl, thiophene-3-yl or bromo), Ar may be 1,4-phenylene and Cy may be thiophene-3-yl.

[00049] In some embodiments, n is 1 and in others it is 2 or 3. In the event that n is 2 or 3, Ar may be 1,4-phenylene and Cy may be thiophene-3-yl or thiazole-2-yl.

[00050] In some embodiments, R^3 and R^4 are either both H or both methyl. In other embodiments, one is H and the other is methyl or ethyl. In the event that they are not both H, Ar may be 1,4-phenylene. Alternatively, if they are not both H, either Ar is 1,4-phenylene or Cy is phenyl or either is thiazole-2-yl.

[00051] In some embodiments R^5 is H.

[00052] In some embodiments Ar is 1,4-phenylene and Cy is thiophene-3-yl or thiazole-2-yl. In particular embodiments Ar is 1,4-phenylene and Cy is thiophene-3-yl.

[00053] In a particular embodiment, R^1 and R^2 are both Me, D is H, n is 1 and R^3 and R^4 are both H. In this embodiment, it is preferred that if Ar is 1,4-phenylene, Cy is not thiophene-3-yl. In a variation of this embodiment, either R^1 and R^2 are not both methyl, or D is not H, or n is not 1, or R^3 and R^4 are not both H (optionally more than one, and in particular instances all, of these

apply) and Ar is 1,4-phenylene and Cy is thiophene-3-yl or thiazole-2-yl (optionally Ar is 1,4-phenylene and Cy is thiophene-3-yl).

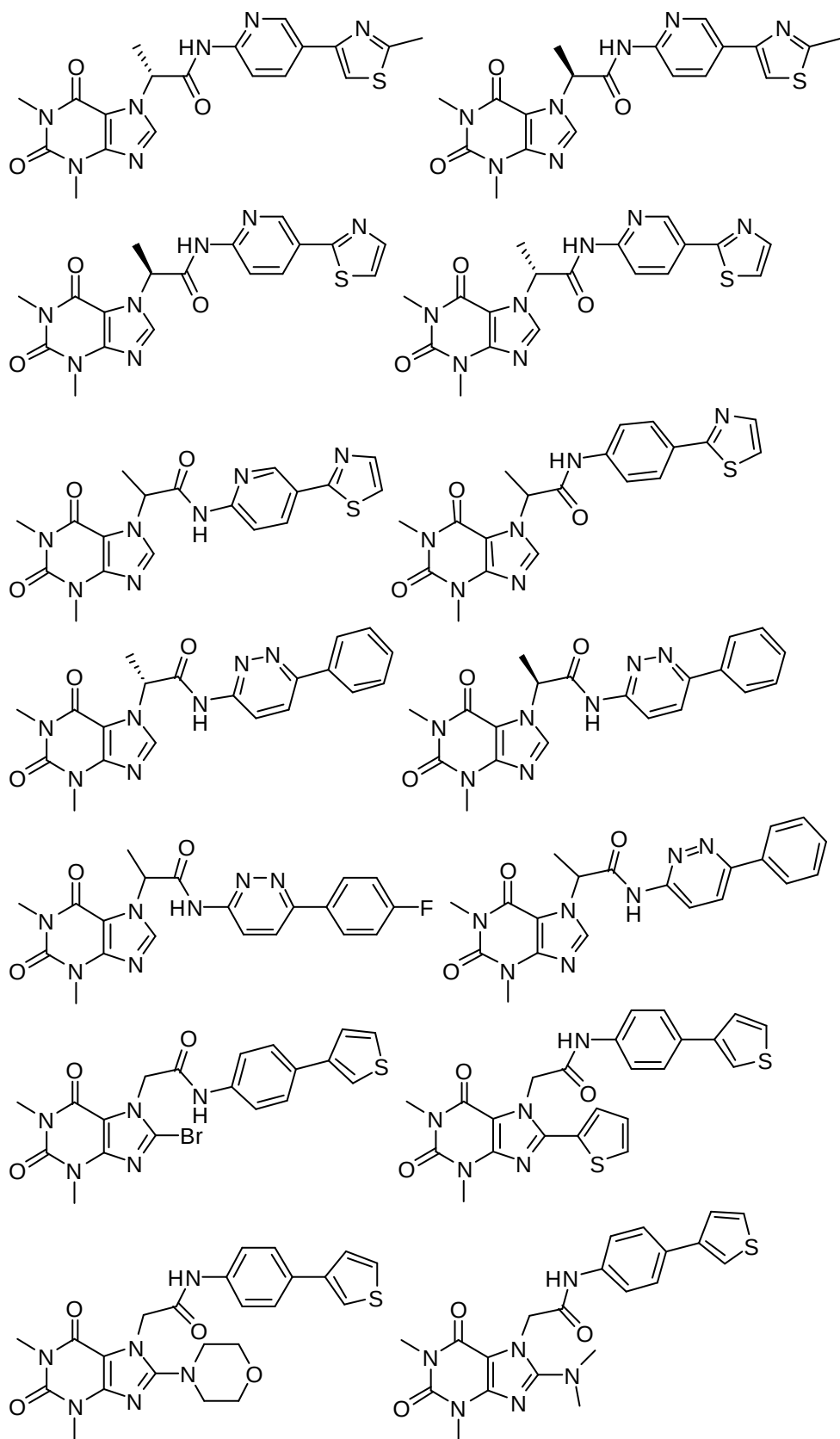
[00054] In some embodiments, any one or more, optionally all, of compounds 7, 13, 27, 28, 39, 42, 43, 44, 58, 65, 71, 80 and 83 as defined hereinafter may be excluded from the scope of the invention. In some embodiments, any one or more, optionally all, of compounds 8, 12, 55 and 85 may also be excluded.

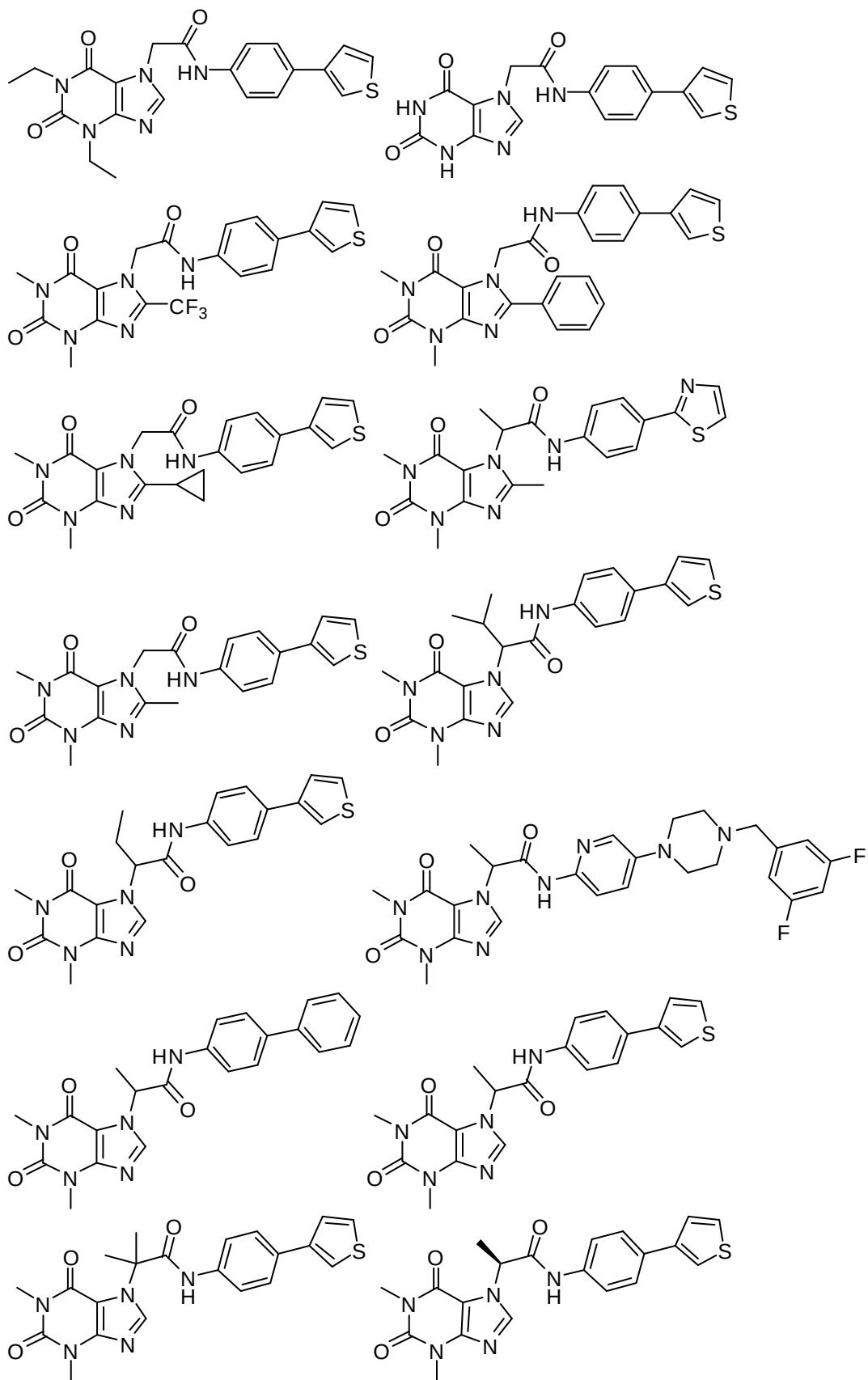
[00055] In some embodiments, Ar and Cy are not both optionally substituted phenyl rings. In some embodiments, at least one of Ar and Cy is heteroaromatic or non-aromatic. In some embodiments at least one of Ar and Cy is heteroaromatic.

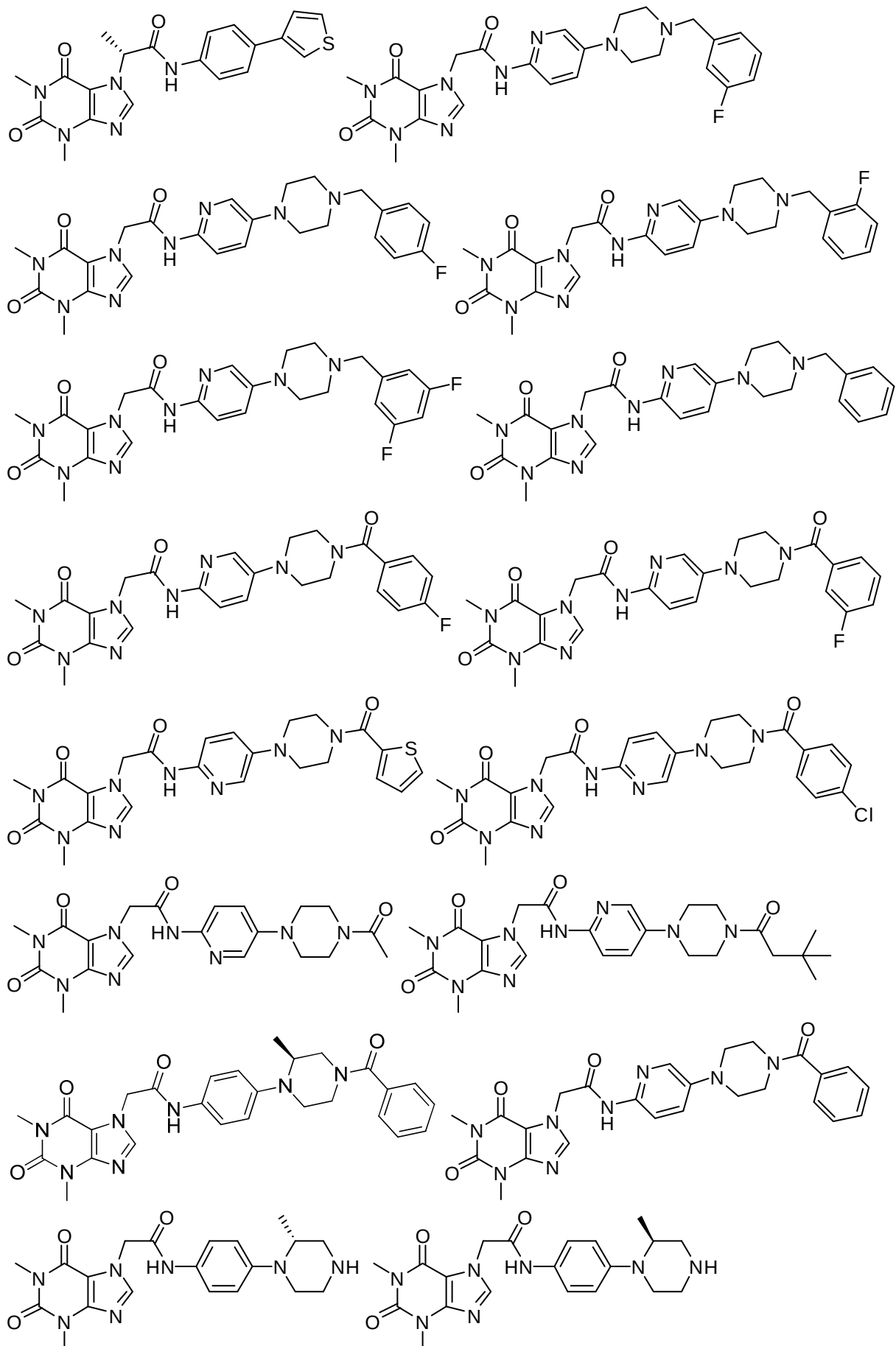
[00056] In some embodiments, if Ar is 1,4-phenylene or 2,5-pyridyl, Cy has no more than 1 ring nitrogen atom. In other embodiments, if Ar is a 5-membered ring, it is not oxazolidiyl. In yet other embodiments, if Ar is a 5-membered ring, it may be thiophenediyl, e.g. thiophene-2,4-diyl. In the context of the present specification, reference to “if A then B” should be taken to indicate the possibilities either that A is not the case or that both A and B are the case. Therefore for example, the statement “if Ar is a 5-membered ring, it may be thiophenediyl” may be taken to mean that either Ar is not a 5-membered ring, or else Ar is a thiophenediyl ring. In such instances, Ar could be for example, a pyridinediyl ring, but could not be a furandiyl ring.

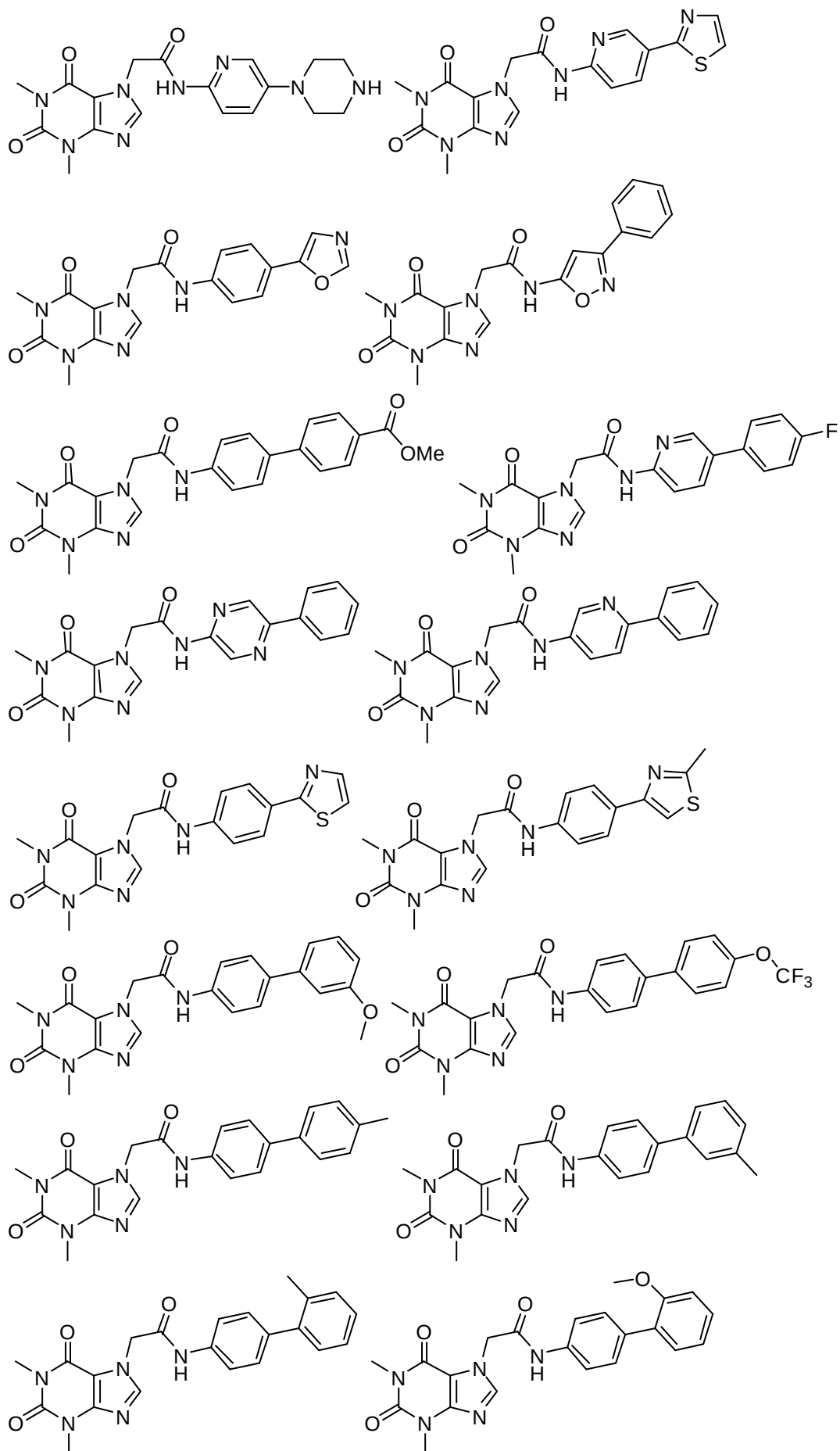
[00057] It will be understood that many (although not all) of the limitations set out above in various embodiments may be used together in combination, and the present invention explicitly contemplates such combinations where they are practicable.

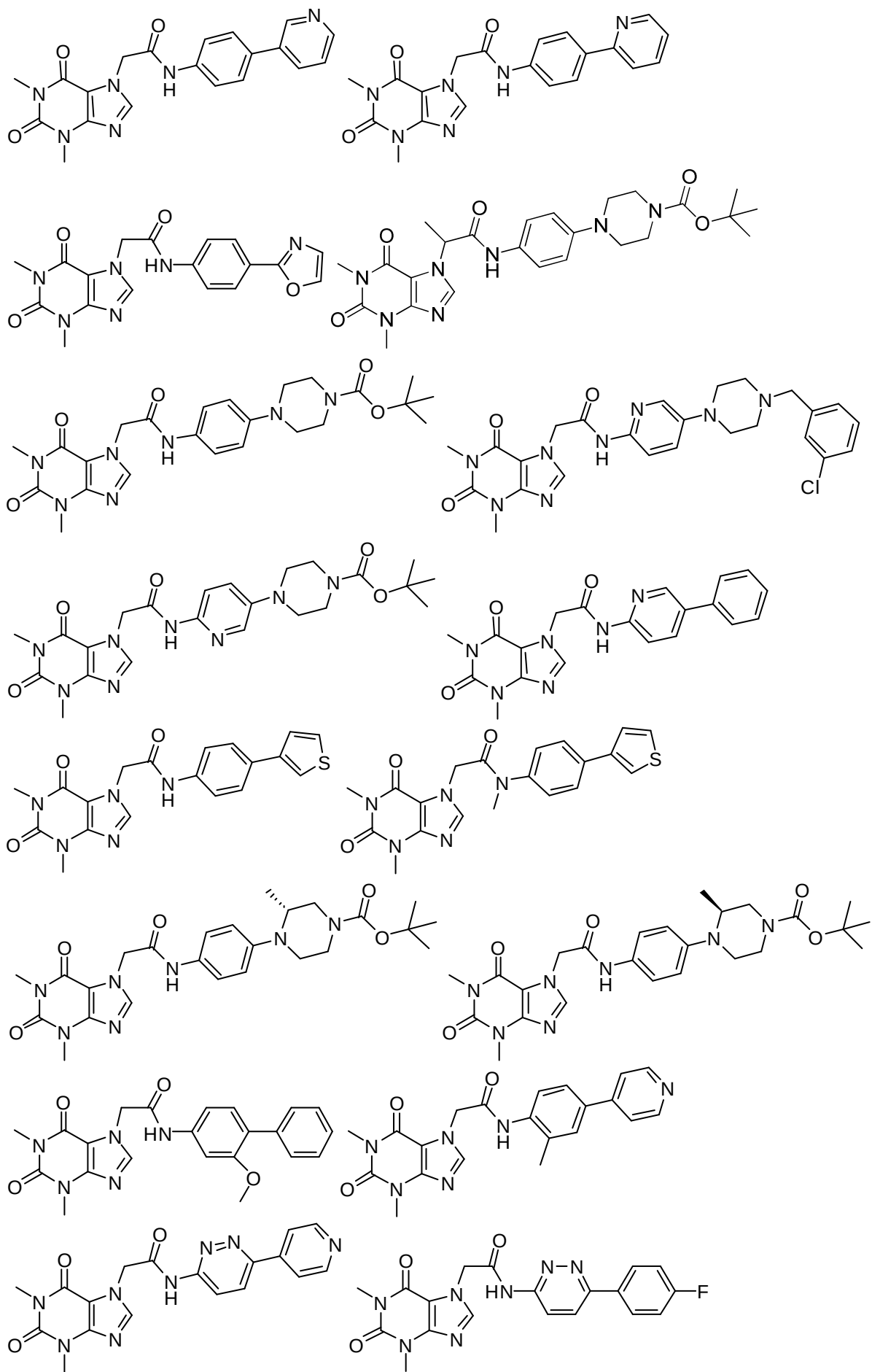
[00058] Specific (but non-limiting) examples of the compounds of the present invention are set out below:

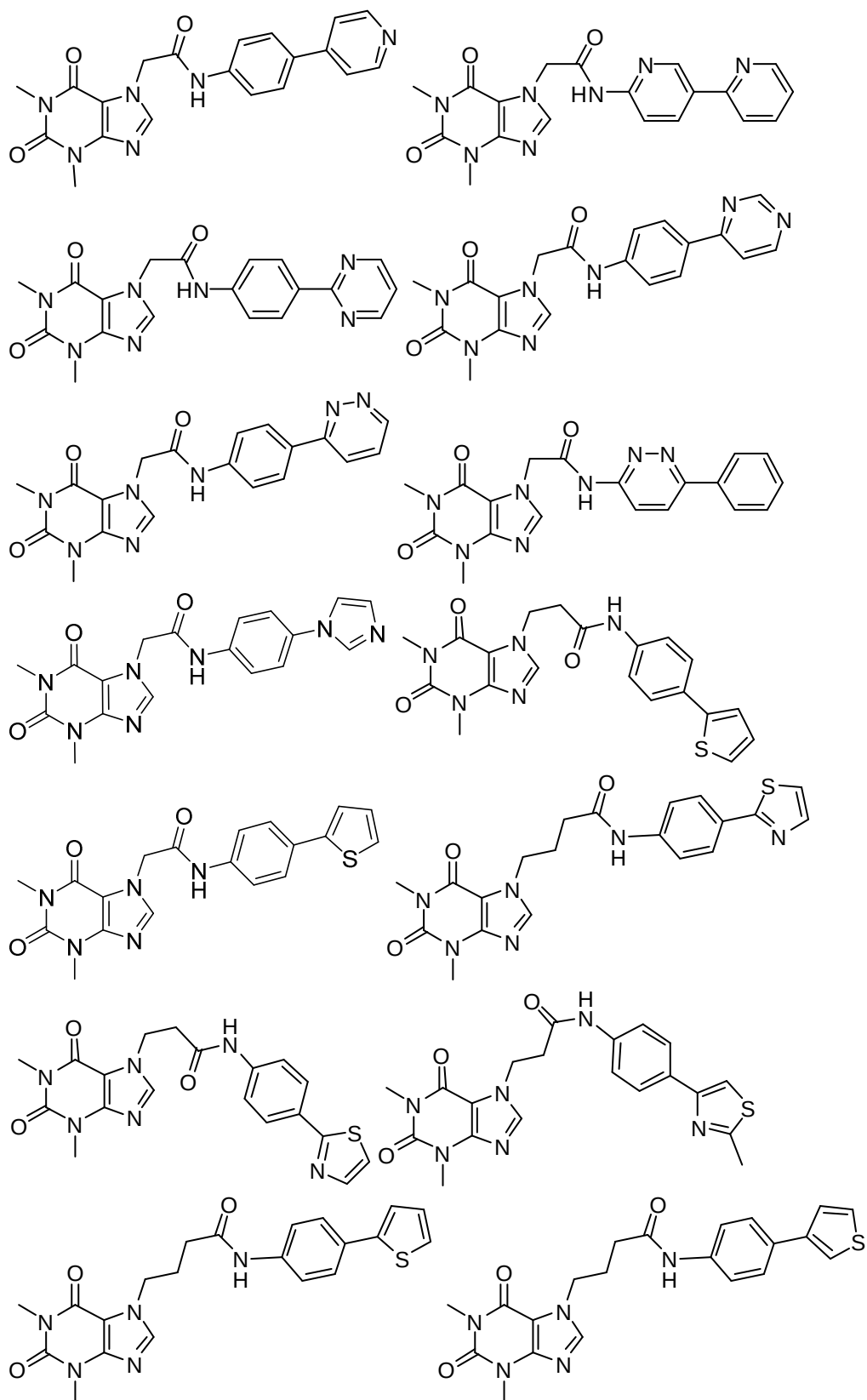


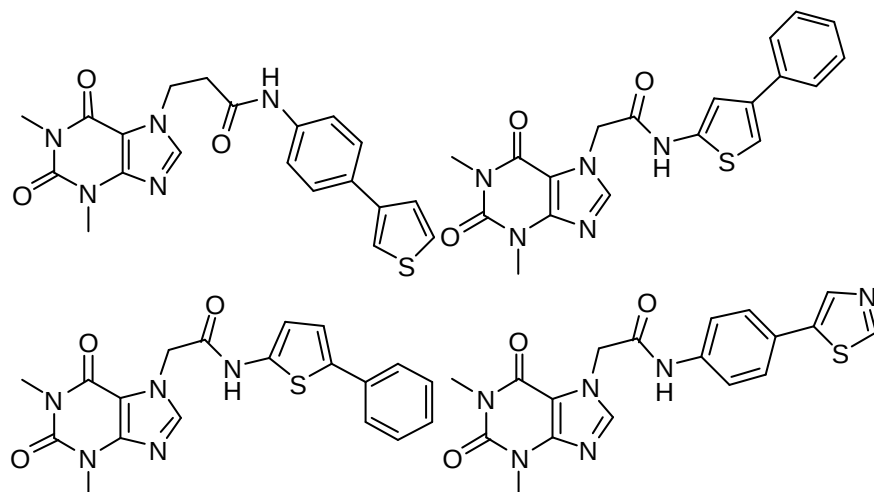












[00059] The compounds of the present invention may have an IC_{50} against STF3A of less than about 10 micromolar. The IC_{50} may be less than about 5, 2, 1, 0.5, 0.2 or 0.1 micromolar. It may be between about 0.01 and about 10 micromolar, or between about 0.01 and 5, 0.01 and 1, 0.01 and 0.5, 0.01 and 0.1, 0.01 and 0.05, 0.1 and 5, 0.1 and 1, 0.1 and 0.5, 0.1 and 10, 0.5 and 10, 1 and 10, 5 and 10, 1 and 5 or 0.1 and 0.5, e.g. about 0.01, 0.02, 0.03, 0.04, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 micromolar. A suitable method for testing IC_{50} is as follows: approximately 5000 cells in 75 μ l culture media are seeded in each well of black 96 well plates and incubated overnight at 37°C. 25 μ l of serially diluted compound is then added to the cells giving final concentration of. After 1 day of treatment, 100 μ l of a luminescent cell viability assay reagent is added to each well and incubated for 10 minutes at room temperature. Luminescence is then measured to determine IC_{50} .

[00060] The compound may be such that it does not modulate, or does not inhibit, TRPA1. It may not inhibit TRPA1 at an IC_{50} of about 10 micromolar or of about 5 micromolar or of about 2 micromolar or of about 1 micromolar. It may be a TRPA1 non-inhibitor. The term not inhibit” in this context may refer to an inhibition of less than about 10%, or less than about 5, 2 or 1% at the specified concentration.

[00061] The compounds of the present invention may inhibit phosphorylation of co-receptor LRP6 in PA-1 teratocarcinoma cells and/or in HPAF-II pancreatic adenocarcinoma cells by greater than about 40% after 4 hours at a concentration of about 2 micromolar. In this context, inhibition of 40% indicates that the concentration of phosphorylated LRP6 after 4 hours is 40% lower than in a control to which no inhibiting compound was added. The inhibition under the specified conditions may be greater than about 40%, or greater than about 45, 50 or 55%, and

may be for example about 40, 45, 50, 55 or 60%. The inhibition may be achieved with a concentration of less than about 3 micromolar, or less than about 2, 1, 0.5, 0.2, 0.1 or 0.05 micromolar, or at a concentration of between about 0.003 and 2 micromolar, or between about 0.003 and 1.5 micromolar, 0.003 and 1 micromolar, 0.003 and 0.5 micromolar, 0.003 and 0.2 micromolar, 0.003 and 0.1 micromolar, 0.003 and 0.05, 0.003 and 0.01, 0.01 and 2, 0.1 and 2, 1 and 2, 0.01 and 0.1, 0.01 and 1, 0.01 and 0.1 and 0.05 or 0.005 and 0.5 micromolar, e.g. at a concentration of about 0.003, 0.005, 0.01, 0.002, 0.05, 0.1, 0.2, 0.5, 1, 1.5 or 2 micromolar.

[00062] The compounds of the present invention may be made as exemplified in the Examples provided herewith. A common method involves coupling 1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione (or suitable derivative such as an acid chloride) with an amine $H_2N-Ar-Cy$ (or a protected derivative of that if Ar or Cy have reactive substituents other than NH_2). This reaction may be conducted in the presence of a suitable amine, commonly a tertiary amine such as HATU and/or triethylamine.

[00063] The present invention encompasses in particular the anhydrous form of the free base of 2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)-N-(6-phenylpyridazin-3-yl)acetamide, pharmaceutical compositions containing the anhydrous form of this free base and methods of use of the anhydrous form of the free base in the treatment of certain medical conditions. This compound is labelled herein as compound 5.

[00064] In the development of a drug in solid state form suitable for scale up and cGMP production and ultimately for clinical and commercial use, an acceptable level of drug activity against the target of interest is only one of the important variables that must be considered. For example, in the formulation of pharmaceutical compositions it is imperative that the pharmaceutically active substance be in a form that can be reliably reproduced in a commercial manufacturing process and which is robust enough to withstand the conditions to which the pharmaceutically active substance is exposed.

[00065] In a manufacturing sense it is important that during commercial manufacture the manufacturing process of the pharmaceutically active substance be such that the same material is reproduced when the same manufacturing conditions are used. In addition it is desirable that the pharmaceutically active substance exists in a solid form where minor changes to the manufacturing conditions do not lead to major changes in the solid form of the pharmaceutically

active substance produced. For example it is important that the manufacturing process produce material having the same crystalline properties on a reliable basis and also produce material having the same level of hydration.

[00066] In addition it is important that the pharmaceutically active substance be stable both to degradation, hygroscopicity and subsequent changes to its solid form. This is important to facilitate the incorporation of the pharmaceutically active ingredient into pharmaceutical formulations. If the pharmaceutically active substance is hygroscopic ("sticky") in the sense that it absorbs water (either slowly or over time) it is almost impossible to reliably formulate the pharmaceutically active substance into a drug as the amount of substance to be added to provide the same dosage will vary greatly depending upon the degree of hydration. Furthermore variations in hydration or solid form ("polymorphism") can lead to changes in physico-chemical properties, such as solubility or dissolution rate, which might in turn lead to inconsistent oral absorption in a patient.

[00067] Accordingly, chemical stability, solid state stability, and "shelf life" of the pharmaceutically active agent are very important factors. In an ideal situation the pharmaceutically active agent and any compositions containing it, should be capable of being effectively stored over appreciable periods of time, without exhibiting a significant change in the physico-chemical characteristics of the active component such as its activity, moisture content, solubility characteristics, solid form and the like.

[00068] In relation to 2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)-N-(6-phenylpyridazin-3-yl)acetamide, initial studies were carried out on the free base, the preferred chemical form, and indicated that polymorphism was prevalent with the compound being found to adopt more than one crystalline form depending upon the manufacturing conditions. In addition it was observed that the moisture content varied from batch to batch.

[00069] Accordingly the inventors have prepared a single polymorphic form of 2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)-N-(6-phenylpyridazin-3-yl)acetamide which overcomes or ameliorates one or more of the above identified problems.

[00070] The present invention therefore encompasses an anhydrous form of the free base (non-hydrated single polymorph) of 2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)-n-(6-phenylpyridazin-3-yl)acetamide.

[00071] The anhydrous free base may be crystalline. The crystalline anhydrous free base shows on X-ray diffraction a peak on the 2theta scale at $22.2^{\circ} \pm 0.5^{\circ}$. It also shows on X-ray diffraction peaks on the 2theta scale at $5.5^{\circ} \pm 0.5^{\circ}$ and $14.2^{\circ} \pm 0.5^{\circ}$. In particular, it shows on X-ray diffraction at least four peaks on the 2theta scale selected from the group consisting of $5.5^{\circ} \pm 0.5^{\circ}$ and $12.5^{\circ} \pm 0.5^{\circ}$, $14.2^{\circ} \pm 0.5^{\circ}$, $16.7^{\circ} \pm 0.5^{\circ}$, $17.7^{\circ} \pm 0.5^{\circ}$, $18.8^{\circ} \pm 0.5^{\circ}$, $22.4^{\circ} \pm 0.5^{\circ}$, $24.2^{\circ} \pm 0.5^{\circ}$ and $31.7^{\circ} \pm 0.5^{\circ}$. Specifically it shows on X-ray diffraction peaks on the 2theta scale of and $5.5^{\circ} \pm 0.5^{\circ}$ and $12.5^{\circ} \pm 0.5^{\circ}$, $14.2^{\circ} \pm 0.5^{\circ}$, $16.7^{\circ} \pm 0.5^{\circ}$, $17.7^{\circ} \pm 0.5^{\circ}$, $18.0^{\circ} \pm 0.5^{\circ}$, $18.8^{\circ} \pm 0.5^{\circ}$, $19.6^{\circ} \pm 0.5^{\circ}$, $20.6^{\circ} \pm 0.5^{\circ}$, $22.4^{\circ} \pm 0.5^{\circ}$, $24.2^{\circ} \pm 0.5^{\circ}$, $24.4^{\circ} \pm 0.5^{\circ}$, $25.0^{\circ} \pm 0.5^{\circ}$, $27.0^{\circ} \pm 0.5^{\circ}$, $27.6^{\circ} \pm 0.5^{\circ}$, $29.8^{\circ} \pm 0.5^{\circ}$, $31.7^{\circ} \pm 0.5^{\circ}$ and $32.2^{\circ} \pm 0.5^{\circ}$.

[00072] The present invention also encompasses a pharmaceutical composition comprising the anhydrous free base as described above. It also encompasses a method of treating or preventing a proliferative disorder comprising administration of a therapeutically effective amount of the anhydrous free base of the invention to a patient in need thereof. In some embodiments the proliferative disorder is cancer. It further encompasses the use of the anhydrous free base of the invention in the treatment of a proliferative disorder such as cancer. It further encompasses the use of the anhydrous free base of the invention in the manufacture of a medicament for the treatment of a proliferative disorder. In some embodiments the proliferative disorder is cancer.

[00073] Disclosed herein are also compositions for the modulation of Wnt activity, optionally for the treatment of a disease or condition associated with Wnt pathway activity. These incorporate the compound of structure I as defined above, together with one or more pharmaceutically acceptable adjuvants, diluents and/or carriers.

[00074] Modulator and inhibitor compounds and agents of the present invention may be administered as compositions either therapeutically or preventively. In a therapeutic application, compositions are administered to a patient already suffering from a disease, in an amount sufficient to cure or at least partially arrest the disease and its complications. The composition should provide a quantity of the compound or agent sufficient to effectively treat the patient.

[00075] The therapeutically effective dose level for any particular patient will depend upon a variety of factors including: the disorder being treated and the severity of the disorder; activity

of the compound or agent employed; the composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the route of administration; the rate of sequestration of the agent or compound; the duration of the treatment; drugs used in combination or coincidental with the treatment, together with other related factors well known in medicine.

[00076] One skilled in the art would be able, by routine experimentation, to determine an effective, non-toxic amount of agent or compound which would be required to treat applicable diseases.

[00077] Generally, an effective dosage is expected to be in the range of about 0.0001mg to about 1000mg per kg body weight per 24 hours; typically, about 0.001mg to about 750mg per kg body weight per 24 hours; about 0.01mg to about 500mg per kg body weight per 24 hours; about 0.1mg to about 500mg per kg body weight per 24 hours; about 0.1mg to about 250mg per kg body weight per 24 hours; about 1.0mg to about 250mg per kg body weight per 24 hours. More typically, an effective dose range is expected to be in the range about 1.0mg to about 200mg per kg body weight per 24 hours; about 1.0mg to about 100mg per kg body weight per 24 hours; about 1.0mg to about 50mg per kg body weight per 24 hours; about 1.0mg to about 25mg per kg body weight per 24 hours; about 5.0mg to about 50mg per kg body weight per 24 hours; about 5.0mg to about 20mg per kg body weight per 24 hours; about 5.0mg to about 15mg per kg body weight per 24 hours.

[00078] Alternatively, an effective dosage may be up to about 500mg/m². Generally, an effective dosage is expected to be in the range of about 25 to about 500mg/m², preferably about 25 to about 350mg/m², more preferably about 25 to about 300mg/m², still more preferably about 25 to about 250mg/m², even more preferably about 50 to about 250mg/m², and still even more preferably about 75 to about 150mg/m².

[00079] Typically, in therapeutic applications, the treatment would commonly be for the duration of the disease state.

[00080] Further, it will be apparent to one of ordinary skill in the art that the optimal quantity and spacing of individual dosages will be determined by the nature and extent of the disease state being treated, the form, route and site of administration, and the nature of the particular

individual being treated. Also, such optimum conditions can be determined by conventional techniques.

[00081] It will also be apparent to one of ordinary skill in the art that the optimal course of treatment, such as, the number of doses of the composition given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

[00082] In general, suitable compositions may be prepared according to methods which are known to those of ordinary skill in the art and accordingly may include a pharmaceutically acceptable carrier, diluent and/or adjuvant.

[00083] These compositions can be administered by standard routes. In general, the compositions may be administered by the parenteral (e.g., intravenous, intraspinal, subcutaneous or intramuscular), oral or topical route. More preferably administration is by the parenteral route.

[00084] The carriers, diluents and adjuvants must be "acceptable" in terms of being compatible with the other ingredients of the composition, and not deleterious to the recipient thereof.

[00085] Examples of pharmaceutically acceptable carriers or diluents are demineralised or distilled water; saline solution; vegetable based oils such as peanut oil, safflower oil, olive oil, cottonseed oil, maize oil, sesame oils, arachis oil or coconut oil; silicone oils, including polysiloxanes, such as methyl polysiloxane, phenyl polysiloxane and methylphenyl polysiloxane; volatile silicones; mineral oils such as liquid paraffin, soft paraffin or squalane; cellulose derivatives such as methyl cellulose, ethyl cellulose, carboxymethylcellulose, sodium carboxymethylcellulose or hydroxypropylmethylcellulose; lower alkanols, for example ethanol or iso-propanol; lower alkanols; lower polyalkylene glycols or lower alkylene glycols, for example polyethylene glycol, polypropylene glycol, ethylene glycol, propylene glycol, 1,3-butylene glycol or glycerin; fatty acid esters such as isopropyl palmitate, isopropyl myristate or ethyl oleate; polyvinylpyrrolidone; agar; carrageenan; gum tragacanth or gum acacia, and petroleum jelly. Typically, the carrier or carriers will form from 10% to 99.9% by weight of the compositions.

[00086] The compositions of the invention may be in a form suitable for administration by injection, in the form of a formulation suitable for oral ingestion (such as capsules, tablets, caplets, elixirs, for example), in an aerosol form suitable for administration by inhalation, such as by intranasal inhalation or oral inhalation, in a form suitable for parenteral administration, that is, subcutaneous, intramuscular or intravenous injection.

[00087] For administration as an injectable solution or suspension, non-toxic parenterally acceptable diluents or carriers can include, Ringer's solution, isotonic saline, phosphate buffered saline, ethanol and 1,2 propylene glycol.

[00088] Some examples of suitable carriers, diluents, excipients and adjuvants for oral use include peanut oil, liquid paraffin, sodium carboxymethylcellulose, methylcellulose, sodium alginate, gum acacia, gum tragacanth, dextrose, sucrose, sorbitol, mannitol, gelatine and lecithin. In addition these oral formulations may contain suitable flavouring and colourings agents. When used in capsule form the capsules may be coated with compounds such as glyceryl monostearate or glyceryl distearate which delay disintegration.

[00089] Adjuvants typically include emollients, emulsifiers, thickening agents, preservatives, bactericides and buffering agents.

[00090] Solid forms for oral administration may contain binders acceptable in human and veterinary pharmaceutical practice, sweeteners, disintegrating agents, diluents, flavourings, coating agents, preservatives, lubricants and/or time delay agents. Suitable binders include gum acacia, gelatine, corn starch, gum tragacanth, sodium alginate, carboxymethylcellulose or polyethylene glycol. Suitable sweeteners include sucrose, lactose, glucose, aspartame or saccharine. Suitable disintegrating agents include corn starch, methylcellulose, polyvinylpyrrolidone, guar gum, xanthan gum, bentonite, alginic acid or agar. Suitable diluents include lactose, sorbitol, mannitol, dextrose, kaolin, cellulose, calcium carbonate, calcium silicate or dicalcium phosphate. Suitable flavouring agents include peppermint oil, oil of wintergreen, cherry, orange or raspberry flavouring. Suitable coating agents include polymers or copolymers of acrylic acid and/or methacrylic acid and/or their esters, waxes, fatty alcohols, zein, shellac or gluten. Suitable preservatives include sodium benzoate, vitamin E, alpha-tocopherol, ascorbic acid, methyl paraben, propyl paraben or sodium bisulphite. Suitable

lubricants include magnesium stearate, stearic acid, sodium oleate, sodium chloride or talc. Suitable time delay agents include glyceryl monostearate or glyceryl distearate.

[00091] Liquid forms for oral administration may contain, in addition to the above agents, a liquid carrier. Suitable liquid carriers include water, oils such as olive oil, peanut oil, sesame oil, sunflower oil, safflower oil, arachis oil, coconut oil, liquid paraffin, ethylene glycol, propylene glycol, polyethylene glycol, ethanol, propanol, isopropanol, glycerol, fatty alcohols, triglycerides or mixtures thereof.

[00092] Suspensions for oral administration may further comprise dispersing agents and/or suspending agents. Suitable suspending agents include sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, poly-vinyl-pyrrolidone, sodium alginate or acetyl alcohol. Suitable dispersing agents include lecithin, polyoxyethylene esters of fatty acids such as stearic acid, polyoxyethylene sorbitol mono- or di-oleate, -stearate or -laurate, polyoxyethylene sorbitan mono- or di-oleate, -stearate or -laurate and the like.

[00093] The emulsions for oral administration may further comprise one or more emulsifying agents. Suitable emulsifying agents include dispersing agents as exemplified above or natural gums such as guar gum, gum acacia or gum tragacanth.

[00094] Methods for preparing parenterally administrable compositions are apparent to those skilled in the art, and are described in more detail in, for example, Remington's Pharmaceutical Science, 15th ed., Mack Publishing Company, Easton, Pa., hereby incorporated by reference herein.

[00095] The composition may incorporate any suitable surfactant such as an anionic, cationic or non-ionic surfactant such as sorbitan esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as siliceous silicas, and other ingredients such as lanolin, may also be included.

[00096] The compositions may also be administered in the form of liposomes. Liposomes are generally derived from phospholipids or other lipid substances, and are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolisable lipid capable of forming liposomes can be used. The compositions in liposome form may contain stabilisers, preservatives, excipients and the

like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art, and in relation to this specific reference is made to: Prescott, Ed., *Methods in Cell Biology*, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 *et seq.*, the contents of which is incorporated herein by reference.

[00097] The oral formulation may be formulated with one or more pharmacologically acceptable ingredients to make a tablet or capsule etc. with an enteric coating. Methods for such formulations are well known to those skilled in the art (see e.g., Remington: *The Science and Practice of Pharmacy*, 19th ed. (1995) Mack Publishing Company, Easton, Pa.; herein incorporated by reference). The enteric coating may be an enteric coating which enhances delivery of the composition or active(s) drugs to specific regions of the gastrointestinal tract for enhanced bioavailability, such as are described in United States of America Patent Application Publication No. 20040162263 entitled "Pharmaceutical formulations targeting specific regions of the gastrointesinal tract" to Sands *et al* and published 19 August 2004.

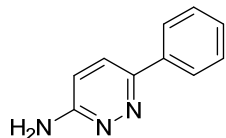
Examples

[00098] The following examples provide compounds according to the present invention together with a number of general synthetic schemes for preparing the compounds. Each synthetic scheme has been illustrated with a specific example, and the examples following that may be made by the same general process. The person skilled in the art will readily appreciate the variations required to the illustrated example of each synthetic scheme in order to prepare other related compounds.

[00099] Synthesis of amines

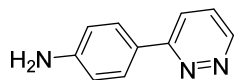
Suzuki Method A: A stirred solution of the arylhalide (1 equiv.), boronic acid (1.5 equiv.) and sodium carbonate (2 equiv.) in toluene (0.08 M) and water (0.32 M) was degassed for 15 min with argon. Tetrakis(triphenylphosphine)palladium(0) (0.05 equiv.) was added to reaction mixture and the reaction mixture was heated to reflux for 16 h. After completion of starting material, the reaction mixture was concentrated and water was added to reaction mixture and extracted with ethyl acetate. The combined organic layers were washed with brine, dried with Na₂SO₄ and concentrated under vacuum. The crude compound was purified by column chromatography to afford the purified product.

[000100] Synthesis of 6-phenylpyridazin-3-amine.



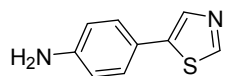
^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.96-7.94 (d, $J=8$ Hz, 2H), 7.82-7.80 (d, $J=9.2$ Hz, 1H), 7.48-7.35 (m, 3H), 6.86-6.84 (m, 1H), 6.64(br s, 2H). LC-MS: m/z 172.0 ($M+H$) with a purity of 82%.

[000101] Synthesis of 4-(pyridazin-3-yl) aniline.



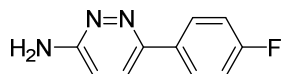
^1H NMR (400 MHz, CDCl_3) δ (ppm): 9.01-9.0 (d, $J=4.4$ Hz, 1H), 8.01-7.99 (d, $J=8.8$ Hz, 1H), 7.88-7.86 (d, $J=7.9$ Hz, 2H), 7.62-7.60 (m, 1H), 6.68-6.66 (d, $J=8.0$ Hz, 2H), 5.61 (s, 2H).

[000102] Synthesis of 4-(thiazol-5-yl)aniline.



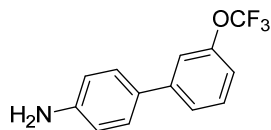
^1H NMR (400 MHz, CDCl_3) δ (ppm): 8.87 (s, 1H), 8.01 (s, 1H), 7.33-7.31 (d, $J=8.4$ Hz, 2H), 6.60-6.58 (d, $J=8.3$ Hz, 2H), 5.42 (s, 2H).

[000103] Synthesis of 6-(4-fluorophenyl)pyridazin-3-amine.



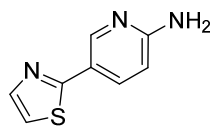
^1H -NMR (400 MHz; DMSO- d_6) δ (ppm): 8.02-7.98 (m, 2H), 7.82 (d, $J=9.2$ Hz, 1H), 7.29 (t, $J=9.2$ Hz, 2H), 6.84 (d, $J=9.6$ Hz, 1H), 6.5 (s, 2H). LC-MS: m/z 190 ($M+H$) with a purity of 99%.

[000104] Synthesis of 3'-(trifluoromethoxy)biphenyl-4-amine.



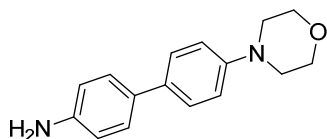
^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.44 – 7.46 (m, 1H), 7.36 – 7.41 (m, 4H), 7.09 – 7.11 (m, 1H), 6.74 – 6.77 (m, 2H), 3.77 (bs, 2H).

[000105] Synthesis of 5-(thiazol-2-yl)pyridin-2-amine.



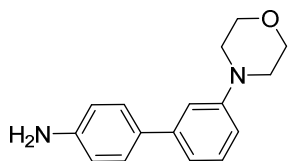
^1H NMR (400 MHz, MeOD- d_4) δ (ppm): 8.48 (s, 1H), 7.95 – 7.98 (m, 1H), 7.77 (d, J = 3.6 Hz, 1H), 7.48 (d, J = 3.6 Hz, 1H), 6.64 – 6.66 (m, 1H). LC-MS: m/z 178 ($M+H$).

[000106] Synthesis of 4'-morpholinobiphenyl-4-amine.



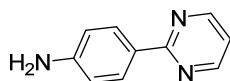
^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.39 (d, J = 8.80 Hz, 2H), 7.26 (d, J = 8.80 Hz, 2H), 6.94 (d, J = 8.80 Hz, 2H), 6.60 (d, J = 8.80 Hz, 2H), 5.06 (s, 2H), 3.74 (t, J = 4.80 Hz, 4H), 3.09 (t, J = 4.80 Hz, 4H).

[000107] Synthesis of 3'-morpholinobiphenyl-4-amine.

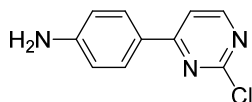


^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.32 – 7.34 (m, 2H), 7.19 – 7.23 (m, 1H), 7.03 (s, 1H), 6.95 – 6.97 (m, 1H), 6.78 – 6.81 (m, 1H), 6.60 – 6.62 (m, 2H), 3.74 (t, J = 4.80 Hz, 4H), 3.14 (t, J = 4.80 Hz, 4H). LC-MS: m/z 255 ($M+H$) with a purity of 88%.

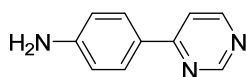
[000108] Synthesis of 4-(pyrimidin-2-yl) aniline.



[000109] Synthesis of 4-(2-chloropyrimidin-4-yl)aniline.



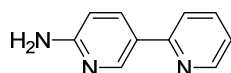
^1H -NMR (400 MHz; DMSO- d_6) δ (ppm): 8.54 (d, J = 5.2 Hz, 1H), 7.92 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 5.2 Hz, 1H), 6.65 (d, J = 8.8 Hz, 2H), 6.04 (s, 2H). MS (ESI): m/z 206 [$M+H$] $^+$. LC-MS: Purity of 99%.



To a stirred solution of 4-(2-chloropyrimidin-4-yl)aniline (1 equiv.) in methanol (0.1 M) and 10% aqueous NaOH (0.24 M) was added 10% Pd/C (20 wt. %) and stirred under Hydrogen balloon pressure at room temperature for 16 h. The reaction mixture was filtered through celite pad and washed with methanol, filtrate concentrated under reduced pressure. The resultant solid was recrystallized with 30% ethyl acetate in petroleum ether to afford 4-(pyrimidin-4-yl)aniline as a pale yellow solid. $^1\text{H-NMR}$ (400 MHz; DMSO- d_6) δ (ppm): 9.02 (s, 1H), 8.62 (d, J = 5.2 Hz, 1H), 7.94 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 5.6 Hz, 1H), 6.65 (d, J = 8.8 Hz, 2H), 5.79 (s, 2H). MS (ESI): m/z 172 [$M+H$] $^+$. LC-MS: Purity of 94%.

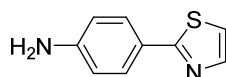
[000110] Suzuki Method B: A solution of aryl halide (1 equiv.) in 1,4-dioxane (0.12 M) and water (0.5 M) was treated with the respective boronic acid or ester (1.2 equiv.), tricyclohexylphosphine (0.1 equiv.) and K_3PO_4 (2 equiv.) at room temperature. Nitrogen gas was passed through the reaction mixture for 15 min. $Pd_2(dba)_3$ (0.1 equiv.) was added to the reaction mixture and degassed for another 15 min. The reaction mixture heated to 100°C for 16 h. After completion, reaction mixture was cooled to room temperature, added water, extracted with ethyl acetate thrice. The combined organic layers were washed with brine solution, dried over anhydrous Na_2SO_4 , filtered, rotary evaporated and dried under vacuum to afford crude product. The crude product was purified by column chromatography to afford the purified product.

[000111] Synthesis of 2,3'-bipyridin-6'-amine.



MS (ESI): m/z 172.13 [$M+H$] $^+$.

[000112] Synthesis of 4-(thiazol-2-yl) aniline.

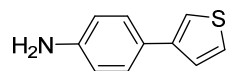


$^1\text{H-NMR}$ (400 MHz; $CDCl_3$) δ (ppm): 7.77 (d, J = 6.0 Hz, 1H), 7.19 (d, J = 3.6 Hz, 1H), 6.71 (d, J = 4.8 Hz, 2H), 3.8 (brs, 2H). LC-MS: m/z 175 [$M-H$] $^-$. Purity of 62%.

[000113] Suzuki Method C: A stirred solution of arylhalide (1.1 equiv.) in 1,4-dioxane (0.7 M) and water (3.5 M) was treated with the respective boronic acid or ester (1 equiv.) and K_2CO_3 (2.4 equiv.) at room temperature. Nitrogen gas was passed through the reaction mixture for 15 min. $Pd(dppf)Cl_2.DCM$ (0.02 equiv.) was added to the reaction mixture and degassed for another

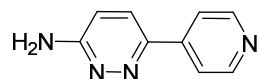
15 minutes. The reaction mixture heated to 100°C for 4 h. After completion, reaction mixture was cooled to room temperature, added water, extracted with ethyl acetate trice. The combined organic layers was washed with brine solution, dried over anhydrous Na₂SO₄, filtered, rotary evaporated and dried under vacuum to afford crude product. The crude product was purified by column chromatography to afford the purified product.

[000114] Synthesis of 4-(thiophen-3-yl) aniline.



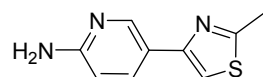
¹H-NMR (400 MHz; CDCl₃) δ (ppm): 7.41 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 3.1 Hz, 1H), 7.32 (d, J = 0.9 Hz, 1H), 7.31 (s, 1H), 6.71 (d, J = 8.4 Hz, 2H), 3.7 (brs, 2H). MS (ESI): m/z 176 [M+H]⁺. LC-MS: Purity of 97 %.

[000115] Synthesis of 6-(pyridin-4-yl) pyridazin-3-amine.



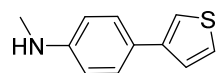
¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 7.96-7.94 (d, J=8 Hz, 2H), 7.82-7.80 (d, J=9.2 Hz, 1H), 7.48-7.35 (m, 3H), 6.86-6.84 (m, 1H), 6.64(br s, 2H). LC-MS: m/z 172.0 (M+H) with a purity of 82%.

[000116] Synthesis of 5-(2-methylthiazol-4-yl)pyridin-2-amine.



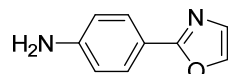
¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.58-8.57 (1H, d, J = 1.6 Hz), 7.94-7.92 (1H, dd, J₁ = 2 Hz, J₂ = 6.4 Hz), 7.15 (1H, s), 6.56-6.54 (1H, d, J = 8.4Hz), 4.54 (2H, brs), 2.76 (3H, s).

[000117] Synthesis of N-methyl-4-(thiophen-3-yl)aniline.



¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.45-7.43 (d, J = 7.0 Hz, 2H), 7.33 (s, 1H), 7.32-7.27 (m, 3H), 6.65-6.63 (d, J = 7.1 Hz, 1H), 3.77-3.58 (brs, 1H), 2.87 (s, 1H).

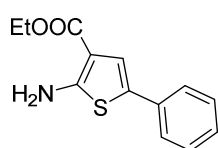
[000118] Synthesis of 4-(oxazol-2-yl) aniline.



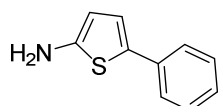
To a solution of commercially available 2-(4-nitrophenyl)oxazole, 1 (1 equiv.) in methanol (0.05 M) was added Pd/C (10% by wt) and stirred reaction at room temperature under H₂ gas balloon pressure for 4 h. After completion of starting material, the reaction mixture was filtered through Celite bed and filtrate was concentrated to give 4-(oxazol-2-yl) aniline, 2 as a brown solid. ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.0 (s, 1H), 7.64 (d, J=8.4 Hz, 2H), 7.20 (s, 1H), 6.63-6.61 (d, J=8.4 Hz, 2H), 5.68 (brs, 2H). LC-MS: m/z 161.0(M+H) with a purity of 97%.

[000119] Synthesis of 5-phenylthiophen-2-amine.

Step 1: Preparation of ethyl 2-amino-5-phenylthiophene-3-carboxylate.



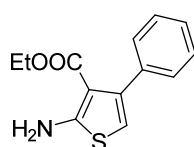
A stirred solution of the respective aldehyde or ketone (1 equiv.), ethyl cyano acetate (1 equiv.) and S powder in ethanol (1.6 M) was treated with morpholine (5 M) dropwise at room temperature and stirred for 3 h. After completion of starting material, the reaction mixture was concentrated and crude compound was purified by column chromatography to give the product. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.45-7.43 (m, 2H), 7.34-7.30 (m, 2H), 7.27-7.20 (m, 2H), 6.0 (brs, 2H), 4.33-4.27 (q, J=7.2 Hz, 2H), 1.39-1.35(t, J=7.2 Hz, 3H). LC-MS: m/z 248.2(M+H) with a purity of 94%.



Step 2: Preparation of 5-phenylthiophen-2-amine.

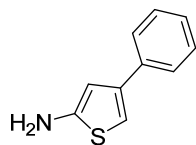
A solution of ethyl 2-amino-5-phenylthiophene-3-carboxylate (1 equiv.) in ethanol (0.04 M) was added 50% aq. HCl (0.04 M) and reaction mixture was heated to reflux for 4 h. After completion of starting material, the reaction mixture was cooled to room temperature and concentrated under vacuum and basified with aq. NaHCO₃ solution and extracted with ethyl acetate twice. The combined organic layers were washed with brine solution dried over NaSO₄ concentrated under vacuum. The crude compound was purified by column chromatography to give the purified product. LC-MS: m/z 176.8(M+H) with a purity of 61%.

[000120] Synthesis of 4-phenylthiophen-2-amine.



Step 1: Preparation of ethyl 2-amino-4-phenylthiophene-3-carboxylate.

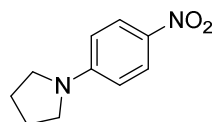
^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.30-7.28 (m, 5H), 6.07 (brs, 1H), 6.05 (brs, 2H), 4.06-4.00 (q, $J=6.8$ Hz, 2H), 0.94-0.91 (t, $J=6.8$ Hz, 3H). LC-MS: m/z 248.03 (M+H) with a purity of 98%.



Step 2: Preparation of 4-phenylthiophen-2-amine.

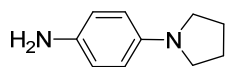
^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 7.60-7.58 (m, 2H), 7.40-7.38 (m, 3H), 7.29-7.27 (m, 2H), 7.15-7.11 (m, 2H). LC-MS: m/z 176.0(M+H) with a purity of 94%.

[000121] Synthesis of 4-(pyrrolidin-1-yl)aniline.



Step 1: Preparation of 1-(4-nitrophenyl)pyrrolidine.

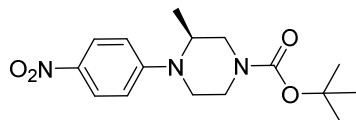
Potassium carbonate (2 equiv.) and the respective amine (1.1 equiv.) were added to a stirred solution of 1-fluoro-4-nitrobenzene, 1 (1 equiv.) in anhydrous DMSO (0.5 M) and stirred at 120°C for 18 h. Upon consumption of starting material, the reaction was diluted with water and extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. Crude product was purified using column chromatography to afford the purified product. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 8.05 (d, $J=9.2$ Hz, 2H), 6.62 (d, $J=9.2$ Hz, 2H), 3.38 (m, 4H), 1.99 (m, 4H). LC-MS: m/z 193 (M+H)



Step 2: Preparation of 4-(pyrrolidin-1-yl)aniline.

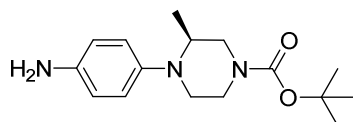
[000122] 1-(4-nitrophenyl)pyrrolidine was dissolved in ethyl acetate (0.05 M) and reduced with H-cube at 50°C , 10 bar. Reduction was completed in 2 cycles. The solvent was evaporated off in vacuo, and the crude purified using column chromatography to afford the product. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 6.49 (d, $J=8.4$ Hz, 2H), 6.34 (d, $J=8.4$ Hz), 4.24 (s, 2H), 3.07 (m, 4H), 1.87 (m, 4H). LC-MS: m/z 163 (M+H).

[000123] Synthesis of (S)-tert-butyl 4-(4-aminophenyl)-3-methylpiperazine-1-carboxylate.



Step 1: Preparation of (S)-tert-butyl 3-methyl-4-(4-nitrophenyl)piperazine-1-carboxylate.

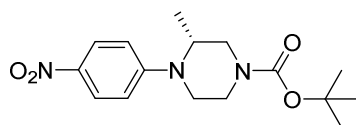
^1H NMR (400 MHz, CDCl_3) δ (ppm): 8.15 - 8.12 (m, 2H), 6.79 - 6.77 (d, $J=9.6$ Hz, 2H), 4.13 - 3.96 (m, 3H), 3.57 - 3.53 (m, 1H), 3.29 - 3.22 (m, 2H), 3.12 (br s, 1H), 1.49 (s, 9H), 1.18 (d, $J=6.4$ Hz, 3H). LC-MS: m/z 363 ($M+H+41$) .



Step 2: Preparation of (S)-tert-butyl 4-(4-aminophenyl)-3-methylpiperazine-1-carboxylate.

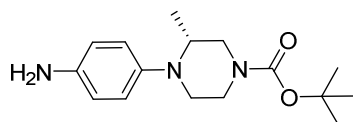
^1H NMR (400 MHz, CDCl_3) δ (ppm): 6.84 (d, $J=8.6$ Hz, 2H), 6.64 (d, $J=8.6$ Hz, 2H), 3.53 (br s, 3H), 3.26 (br s, 2H), 2.99 - 2.96 (m, 1H), 2.88 - 2.85 (m, 1H), 1.48 (s, 9H), 0.87 (d, $J=6.4$ Hz, 3H). LC-MS: m/z 292 ($M+H$).

[000124] Synthesis of (R)-tert-butyl 4-(4-aminophenyl)-3-methylpiperazine-1-carboxylate.



Step 1: Preparation of (R)-tert-butyl 3-methyl-4-(4-nitrophenyl)piperazine-1-carboxylate.

^1H NMR (400 MHz, CDCl_3) δ (ppm): 8.15 - 8.13 (m, 2H), 6.79 - 6.77 (m, 2H), 4.12 (br s, 2H), 4.02 (br s, 1H), 3.57 - 3.53 (m, 1H), 3.29 - 3.22 (m, 2H), 3.12 (br s, 1H), 1.49 (s, 9H), 1.18 (d, $J=6.8$ Hz, 3H). LC-MS: m/z 363 ($M+H+41$).



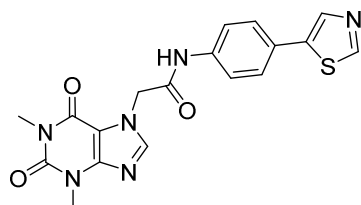
Step 2: Preparation of (R)-tert-butyl 4-(4-aminophenyl)-3-methylpiperazine-1-carboxylate.

^1H NMR (400 MHz, CDCl_3) δ (ppm): 6.84 (d, $J=8.4$ Hz, 2H), 6.65 - 6.63 (m, 2H), 3.53 (br s, 3H), 3.26 (br s, 2H), 2.99 - 2.96 (m, 1H), 2.88 - 2.85 (m, 1H), 1.48 (s, 9H), 0.87 (d, $J=6$ Hz, 3H). LC-MS: m/z 292 ($M+H$).

[000125] Amide coupling Method A: To a stirred solution of commercially available 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetic acid, 1 (1 equiv.) in dichloromethane (0.01 M) was added HATU (1.3 equiv.), triethylamine (1.5 equiv.) and the respective amine (1 equiv.). The reaction mixture was allowed to stir at room temperature. Upon completion of the reaction, water was added to the reaction mixture and the mixture was extracted with

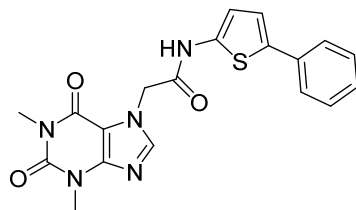
dichloromethane. The organic layer was washed with brine solution, dried over anhydrous Na_2SO_4 , and concentrated under vacuum to afford the crude product. The crude product is further purified by column chromatography.

[000126] Compound 1: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiazol-5-yl)phenyl)acetamide.



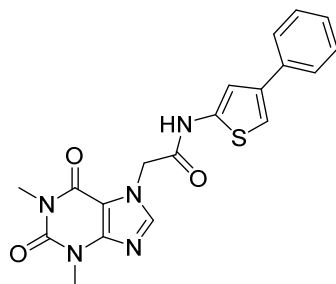
^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 10.58 (s, 1H), 9.03 (s, 1H), 8.24 (s, 1H), 8.08 (s, 1H), 7.65 (s, 4H), 5.20 (s, 2H), 3.40 (s, 3H), 3.20 (s, 3H).

[000127] Compound 2: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(5-phenyl thiophen-2-yl)acetamide.



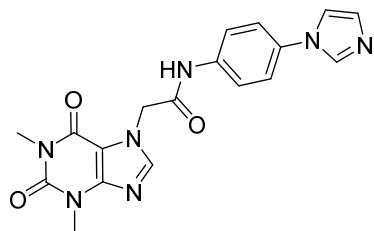
^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 11.71 (s, 1H), 8.09 (s, 1H), 7.55-7.53 (d, $J = 8$ Hz, 2H), 7.38-7.34 (t, $J = 7.6$ Hz, 2H), 7.28-7.21 (m, 2H), 6.73-6.72 (d, $J = 3.6$ Hz, 1H), 5.25 (s, 2H), 3.46 (s, 3H), 3.20 (s, 3H). LC-MS: m/z 396.03 ($\text{M}+\text{H}$) with a purity of 99.02 %. HPLC: At 254 nm with a purity of 95%.

[000128] Compound 3: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-phenyl thiophen-2-yl)acetamide.



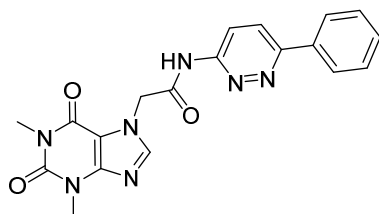
^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 11.70 (s, 1H), 8.09 (s, 1H), 7.64-7.62 (d, J = 7.6 Hz, 2H), 7.42-7.38 (t, J =7.2 Hz, 2H), 7.31-7.28 (m, 2H), 7.08-7.07 (d, J =1.6 Hz, 1H), 5.26 (s, 2H), 3.46 (s, 3H), 3.20 (s, 3H). LC-MS: m/z 396.11 ($M+H$) with a purity of 99%.

[000129] Compound 4: N-(4-(1H-imidazol-1-yl)phenyl)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamide.



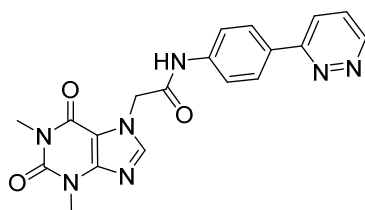
^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.57 (s, 1H), 8.18 (s, 1H), 8.08 (s, 1H), 7.68 – 7.70 (m, 3H), 7.59 – 7.61 (m, 2H), 7.08 (s, 1H), 5.22 (s, 2H), 3.46 (s, 3H), 3.20 (s, 3H). LC-MS: m/z 380 ($M+H$) with a purity of 99%.

[000130] Compound 5: 2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)-N-(6-phenylpyridazin-3-yl)acetamide (alternatively named 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(6-phenyl pyridazin-3-yl)acetamide).



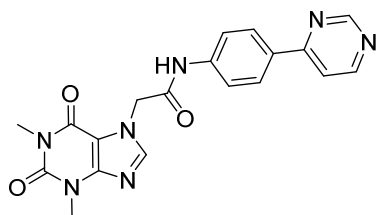
^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 11.77 (s, 1H), 8.32-8.25 (m, 2H), 8.12-8.10 (m, 3H), 7.57-7.49 (m, 3H), 5.37 (s, 2H), 3.46 (s, 3H), 3.19 (s, 3H). LC-MS: m/z 390.1 ($M+H$) with a purity of 99%.

[000131] Compound 6: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(pyridazin-3-yl)phenyl)acetamide.



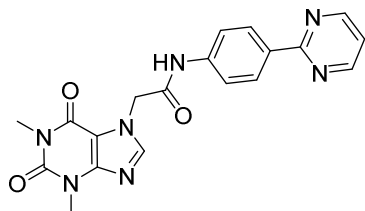
^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.66 (s, 1H), 9.17-9.16 (d, J = 4.4, 1H), 8.20-8.14 (m, 3H), 8.09(s, 1H), 7.77-7.73 (m, 3H), 5.25 (s, 2H), 3.47 (s, 3H), 3.27 (s, 3H), 3.20 (s, 3H). LC-MS: m/z at 392 $[\text{M}+\text{H}]$ with 99%.

[000132] Compound 7: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(pyridazin-3-yl)phenyl)acetamide.



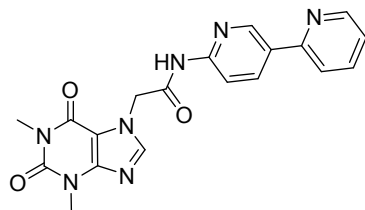
[000133] ^1H -NMR (400 MHz; DMSO- d_6) δ (ppm): 10.65 (brs, 1H), 9.18 (s, 1H), 8.80 (d, J = 5.2 Hz, 1H), 8.20 (d, J = 8.8 Hz, 2H), 8.07 (s, 1H), 8.02 (d, J = 5.2 Hz, 1H), 7.75 (d, J = 8.8 Hz, 2H), 5.25 (s, 2H), 3.46 (s, 3H), 3.20 (s, 3H). MS (ESI): m/z 392 $[\text{M}+\text{H}]^+$. LC-MS: Purity of 97%.

[000134] Compound 8: 2-(1, 3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(pyrimidin-2-yl)phenyl)acetamide.



^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.66 (s, 1H), 8.87-8.86 (d, J = 4.0 Hz, 2H), 8.37-8.35 (d, J = 8.4 Hz, 2H), 8.08 (s, 1H), 7.74-7.72 (d, J = 8.8 Hz, 2H), 7.40-7.38 (t, J = 4.8 Hz, 1H), 5.24 (s, 2H), 3.46 (s, 3H), 3.20 (s, 3H). LC-MS: m/z at 392 $[\text{M}+\text{H}]$ with 99%.

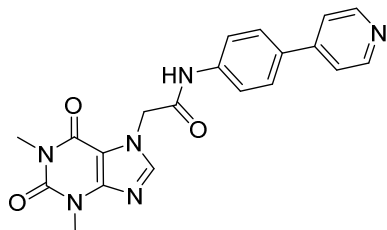
[000135] Compound 9: N-(2,3'-bipyridin-6'-yl)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamide.



^1H -NMR (400 MHz; DMSO- d_6) δ (ppm): 11.21 (s, 1H), 9.08 (s, 1H), 8.67 (d, J = 3.4 Hz, 1H), 8.47 (d, J = 7.2 Hz, 1H), 8.08 (s, 1H), 8.03 (d, J = 7.2 Hz, 2H), 7.9 (t, J = 7.6 Hz, 1H), 7.38 (t, J

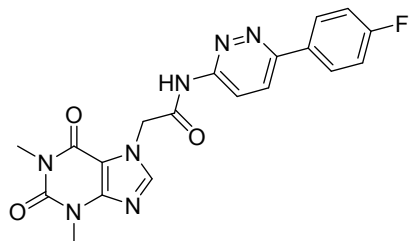
= 5.2 Hz, 1H), 5.30 (s, 2H), 3.46 (s, 3H), 3.19 (s, 3H). MS (ESI): m/z 392.13 $[M+H]^+$. LC-MS: Purity of 97%.

[000136] Compound 10: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(pyridin-4-yl)phenyl)acetamide.



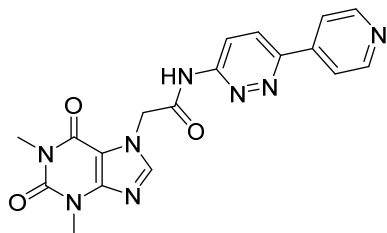
^1H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.55 (d, $J = 6.00$ Hz, 2H), 7.992 (s, 1H), 7.73 – 7.78 (m, 4H), 7.71 (d, $J = 6.00$ Hz, 2H), 5.28 (s, 2H), 3.58 (s, 3H), 3.33 (s, 3H). LC-MS: m/z 391 ($M+H$) with a purity of 99%.

[000137] Compound 11: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(6-(4-fluoro phenyl)pyridazin-3-yl)acetamide.



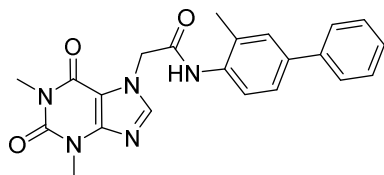
^1H -NMR (400 MHz; CDCl_3) δ (ppm): 11.65 (s, 1H), 8.58 (d, $J = 9.6$ Hz, 1H), 7.99 (dd, $J = 5.2$ Hz, $J = 3.6$ Hz, 2H), 7.90 (d, $J = 9.2$ Hz, 1H), 7.73 (s, 1H), 7.17 (t, $J = 8.8$ Hz, 1H), 5.57 (s, 2H), 3.64 (s, 3H), 3.42 (s, 3H). MS (ESI): m/z 410.17 $[M+H]^+$. LC-MS: Purity of 99%.

[000138] Compound 12: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(6-(pyridin-4-yl)pyridazin-3-yl)acetamide.



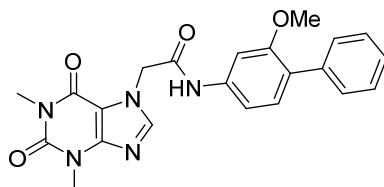
^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.88 (brs, 1H), 8.76 (s, 2H), 8.39-8.37 (m, 2H), 8.15-8.09 (m, 3H), 5.38 (s, 2H), 3.46 (s, 3H), 3.19 (s, 3H). LC-MS: m/z 393.20 ($M+H$) with a purity of 98.93 %. HPLC: At 254 nm with a purity of 98%.

[000139] Compound 13: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(3-methyl biphenyl-4-yl)acetamide.



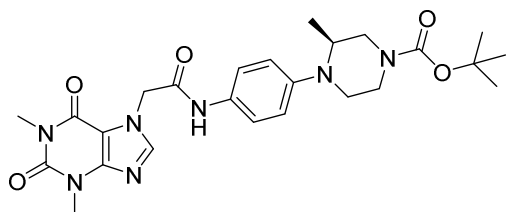
^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 9.79 (s, 1H), 8.10 (s, 1H), 7.63 (d, J = 7.6 Hz, 2H), 7.54-7.40 (m, 5H), 7.34 (t, J = 7.2 Hz, 1H), 5.26 (s, 2H), 3.45 (s, 3H), 3.22 (s, 3H), 2.32 (s, 3H).

[000140] Compound 14: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(2-methoxy biphenyl-4-yl)acetamide.



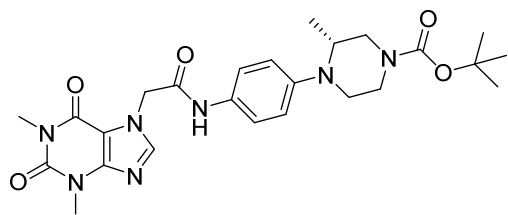
^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.56 (s, 1H), 8.09 (s, 1H), 7.48-7.30 (m, 5H), 7.28-7.17 (m, 3H), 5.23 (s, 2H), 3.72 (s, 3H), 3.46 (s, 3H), 3.20 (s, 3H).

[000141] Compound 15: (S)-tert-butyl 4-(4-(2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamido)phenyl)-3-methylpiperazine-1-carboxylate.



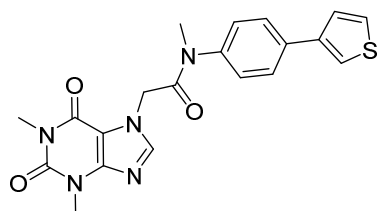
^1H NMR (400 MHz, CDCl_3) δ (ppm): 9.27 (s, 1H), 7.77 (s, 1H), 7.42 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 4.94 (s, 2H), 4.00 - 3.78 (br s, 1H), 3.71 - 3.69 (m, 2H), 3.61 (s, 3H), 3.46 (s, 3H), 3.42 - 3.36 (m, 1H), 3.21 (br s, 1H), 3.05 - 3.03 (m, 2H), 1.47 (s, 9H), 0.94 (d, J = 6.4 Hz, 3H). LC-MS: m/z 512 ($M+H$) with a purity of 97%.

[000142] Compound 16: (R)-tert-butyl 4-(4-(2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamido)phenyl)-3-methylpiperazine-1-carboxylate.



^1H NMR (400 MHz, CDCl_3) δ (ppm): 9.35 (br s, 1H), 7.77 (s, 1H), 7.46 – 7.44 (m, 2H), 6.90 (br s, 2H), 4.94 (s, 2H), 3.89 (br s, 1H), 3.70 – 3.68 (m, 1H), 3.67 – 3.61 (m, 4H), 3.46 (m, 4H), 3.32 – 3.25 (br s, 1H), 3.09 (br s, 2H), 1.48 (s, 9H), 0.96 (d, $J=6.4$ Hz, 3H). LC-MS: m/z 512 ($\text{M}+\text{H}$) with a purity of 97%.

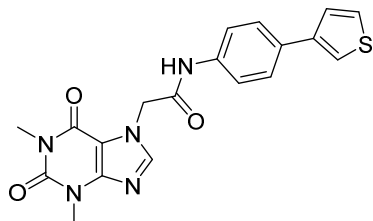
[000143] Compound 17: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-methyl-N-(4-(thiophen-3-yl)phenyl)acetamide.



^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.74-7.72 (d, $J=7.6$ Hz, 2H), 7.54-7.51 (d, $J=9.2$ Hz, 2H), 7.43-7.26 (m, 4H), 4.89 (s, 2H), 3.59 (s, 3H), 3.38 (s, 3H), 3.34 (s, 3H). MS (ESI) m/z 410 [$\text{M}+1$].

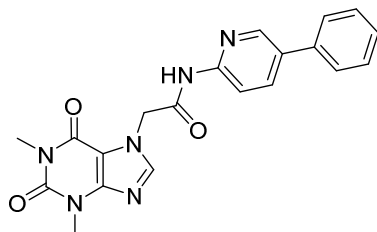
[000144] Amide coupling Method B: To a stirred solution of commercially available 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetic acid, 1 in N,N-dimethylformamide (0.2 M) was added Hunig's base (1.5 equiv.), HATU (1.5 equiv.) and the respective amine (1.2 equiv.). The mixture was stirred at room temperature. After consumption of starting material, the reaction mixture was quenched with water and extracted with dichloromethane. The combined organic layers were washed with brine solution, dried over Na_2SO_4 and concentrated under vacuum to afford the crude product. The crude product is further purified by column chromatography.

[000145] Compound 18: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl)acetamide.



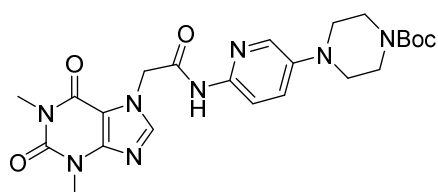
^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.43 (s, 1H), 8.07 (s, 1H), 7.78 - 7.77 (m, 1H), 7.69 - 7.67 (m, 2H), 7.62 - 7.60 (m, 3H), 7.53 - 7.52 (m, 1H), 5.22 (s, 2H), 3.47 (s, 3H), 3.21 (s, 3H).
LC-MS: m/z 396 ($\text{M}+\text{H}$) with a purity of 98%.

[000146] Compound 19: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(5-phenylpyridin-2-yl)acetamide.



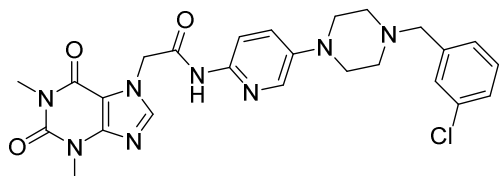
^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.07 (bs, 1H), 8.68 (s, 1H), 8.04 - 8.12 (m, 3H), 7.70 - 7.72 (m, 2H), 7.48 (t, $J = 7.60$ Hz, 2H), 7.38 (t, $J = 7.60$ Hz, 1H), 5.29 (s, 2H), 3.19 (s, 3H).
LC-MS: m/z 391 ($\text{M}+\text{H}$) with a purity of 98%.

[000147] Compound 20: tert-butyl 4-(4-(2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl) propanamido)phenyl)piperazine-1-carboxylate.



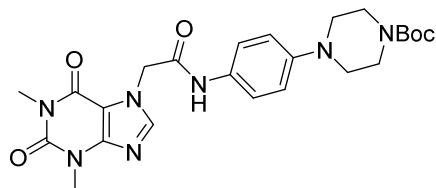
^1H NMR (600 MHz, C_6D_6) δ (ppm): 9.84 (s, 1H), 8.39 (d, $J = 9.0$ Hz, 1H), 7.92 (d, $J = 2.9$ Hz, 1H), 7.01 (s, 1H), 6.64 (dd, $J = 9.0, 2.9$ Hz, 1H), 4.35 (s, 2H), 3.26 (m, 4H), 3.26 (s, 3H), 3.25 (s, 3H), 2.53 - 2.40 (m, 4H), 1.45 (s, 10H). LC-MS: m/z 499 ($\text{M} + \text{H}$) with a purity of 99%

[000148] Compound 21: N-(5-(4-(3-chlorobenzyl)piperazin-1-yl)pyridin-2-yl)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamide.



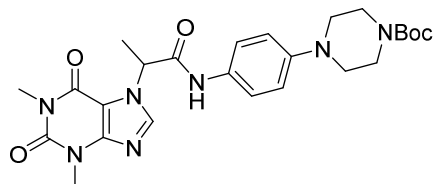
^1H NMR (600 MHz, CDCl_3) δ (ppm): 9.43 (s, 1H), 8.01 – 7.94 (m, 2H), 7.74 (s, 1H), 7.36 (s, 1H), 7.24 (ddd, J = 12.1, 7.6, 3.3 Hz, 4H), 5.09 (s, 2H), 3.60 (s, 3H), 3.54 (s, 2H), 3.42 (s, 3H), 3.22 – 3.14 (m, 4H), 2.65 – 2.57 (m, 4H). LC- MS: m/z 523 ($M + H$), 521($M-H$) with a purity of 98%.

[000149] Compound 22: tert-butyl 4-(4-(2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamido)phenyl)piperazine-1-carboxylate.



^1H NMR (600 MHz, CDCl_3) δ (ppm): 9.30 (s, 1H), 7.77 (s, 1H), 7.42 (d, J = 9.1 Hz, 2H), 6.87 (d, J = 8.9 Hz, 2H), 4.95 (s, 2H), 3.60 (s, 3H), 3.57 (m, 4H), 3.45 (s, 3H), 3.07 (m, 4H), 1.47 (s, 9H). LC-MS: m/z 498 ($M + 1$), 496 ($M-1$) with purity of 99%.

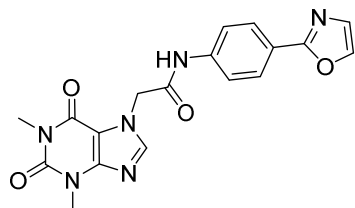
[000150] Compound 23: tert-butyl 4-(4-(2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl) propanamido)phenyl)piperazine-1-carboxylate.



^1H NMR (600 MHz, MeOD-d_4) δ (ppm): 8.23 (s, 1H), 7.83 (s, 2H), 7.51 (d, J = 7.6 Hz, 2H), 7.00 (d, J = 7.6 Hz, 2H), 5.81 (q, J = 7.2 Hz, 1H), 3.64 (bs, 7H), 3.39 (s, 3H), 3.15 (m, 4H), 1.96 (d, J = 7.2 Hz, 3H), 1.55 (s, 9H). LC-MS: m/z 512 ($M + 1$), 510($M-1$) with purity of 98%.

[000151] Amide coupling Method C: To a stirred solution of commercially available 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetic acid, 1 in dichloromethane (0.1 M) was added the respective amine (100 1 equiv.), EDCI (1.2 equiv.) and HOBT (1.2 equiv.). The reaction mixture was stirred at room temperature for 16 h. After completion of starting material, water was added to the reaction mixture and product was extracted with 10% methanol/chloroform twice. The organic layer was dried over anhydrous Na_2SO_4 , concentrated under vacuum to afford the crude product. The crude product is further purified by column chromatography.

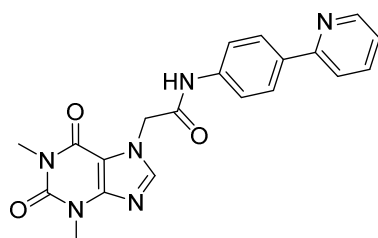
[000152] Compound 24: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(oxazol-2-yl) phenyl)acetamide.



^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.72 (s, 1H), 8.19 (s, 1H), 8.09 (s, 1H), 7.96-7.94 (d, J = 8.8 Hz, 2H), 7.75-7.72 (d, J = 8.8 Hz, 2H), 7.35 (s, 1H), 5.24 (s, 2H), 3.46 (s, 3H), 3.19 (s, 3H). LC-MS: m/z 379.3 ($M+H$) with a purity of 96.48 %. HPLC: At 254 nm with a purity of 97%.

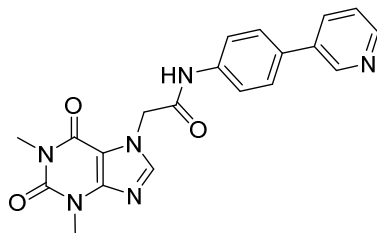
[000153] Amide coupling Method D: A stirred solution of commercially available 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetic acid, 1 (1 equiv.) in N,N -dimethylformamide (0.18 M), was added Hunig's base (1.5 equiv.), HOBT (1.5 equiv.), EDCI (1.5 equiv.) and the respective amine (1.5 equiv.). The mixture was stirred at room temperature for 16 h. After consumption of starting material, the reaction mixture was quenched with water and extracted with dichloromethane. The combined organic layers were washed with brine solution, dried over Na_2SO_4 and concentrated under vacuum. The crude compound was purified by column chromatography to afford the product.

[000154] Compound 25: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(pyridin-2-yl) phenyl)acetamide.



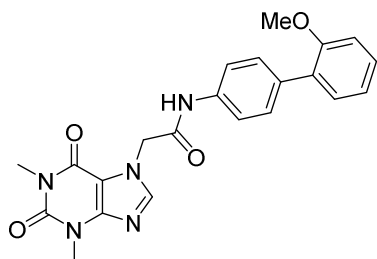
^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.57 (s, 1H), 8.61 – 8.62 (m, 1H), 8.05 – 8.08 (m, 3H), 7.91 (d, J = 8.00 Hz, 1H), 7.82 – 7.86 (m, 1H), 7.68 (d, J = 8.00 Hz, 1H), 7.28 – 7.31 (m, 1H), 5.23 (s, 2H), 3.46 (s, 3H), 3.20 (s, 3H).

[000155] Compound 26: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(pyridin-3-yl)phenyl)acetamide.



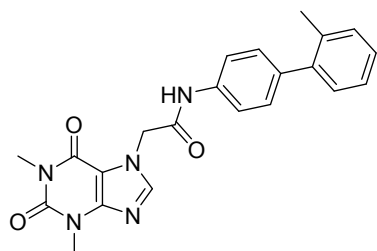
^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.56 (s, 1H), 8.87 (s, 1H), 8.52 – 8.53 (m, 1H), 8.08 (s, 1H), 8.04 – 8.06 (m, 1H), 7.68 – 7.73 (m, 4H), 7.44 – 7.47 (m, 1H), 5.23 (s, 2H), 3.46 (s, 3H), 3.20 (s, 3H). LC-MS: m/z 391 ($M+H$) with a purity of 97%.

[000156] Compound 27: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(2'-methoxy biphenyl-4-yl)acetamide.



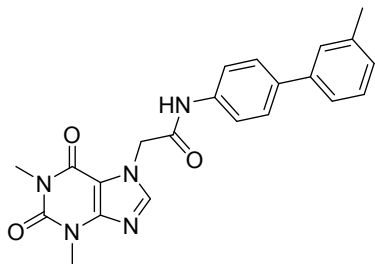
^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.48 (s, 1H), 8.08 (s, 1H), 7.60 - 7.58 (m, 2H), 7.44 - 7.42 (m, 2H), 7.33 - 7.25 (m, 2H), 7.08 (d, $J=8$ Hz, 1H), 7.00 (t, $J=7.4$ Hz, 1H), 5.21 (s, 2H), 3.74 (s, 3H), 3.20 (s, 3H). LC-MS: m/z 420 ($M+H$) with a purity of 98%

[000157] Compound 28: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(2'-methyl biphenyl-4-yl)acetamide.



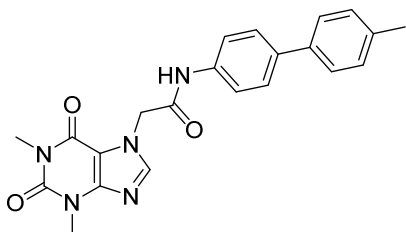
^1H NMR (400 MHz, MeOD- d_4) δ (ppm): 8.00 (s, 1H), 7.63 - 7.61 (m, 2H), 7.28 - 7.23 (m, 3H), 7.22 - 7.19 (m, 2H), 7.18 - 7.15 (m, 1H), 5.28 (s, 2H), 3.58 (s, 3H), 3.35 (s, 3H), 2.24 (s, 3H). LC-MS: m/z 404 ($M+H$) with a purity of 98%.

[000158] Compound 29: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(3'-methyl biphenyl-4-yl)acetamide.



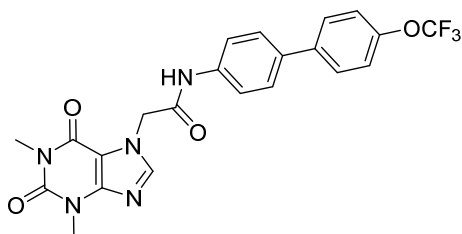
^1H NMR (400 MHz, MeOD-d_4) δ (ppm): 7.99 (s, 1H), 7.65 - 7.63 (m, 2H), 7.58 - 7.56 (m, 2H), 7.41 (s, 1H), 7.38 - 7.36 (m, 1H), 7.29 (t, $J=7.8$, 1H), 7.14 - 7.12 (m, 1H), 5.27 (s, 2H), 3.58 (s, 3H), 3.34 (s, 3H), 2.39 (s, 3H). LC-MS: m/z 404 ($\text{M}+\text{H}$) with a purity of 97%.

[000159] Compound 30: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4'-methyl biphenyl-4-yl)acetamide.



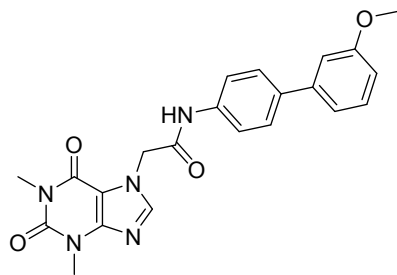
^1H NMR (400 MHz, MeOD-d_4) δ (ppm): 7.99 (s, 1H), 7.64 - 7.62 (m, 2H), 7.57 - 7.55 (m, 2H), 7.48 (d, $J=8$ Hz, 2H), 7.23 (d, $J=8$ Hz, 2H), 5.27 (s, 2H), 3.58 (s, 3H), 3.34 (s, 3H), 2.36 (s, 3H). LC-MS: m/z 404 ($\text{M}+\text{H}$) with a purity of 97%.

[000160] Compound 31: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4'-(trifluoro methoxy)biphenyl-4-yl)acetamide.



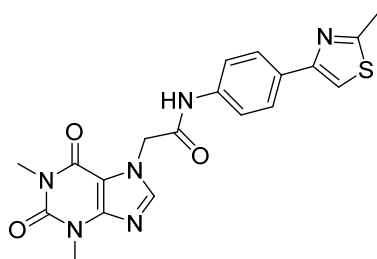
^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.54 (s, 1H), 8.08 (s, 1H), 7.76 (d, $J = 8.40$ Hz, 2H), 7.65 - 7.70 (m, 4H), 7.42 (d, $J = 8.40$ Hz, 2H), 5.23 (s, 2H), 3.46 (s, 3H), 3.20 (s, 3H). LC-MS: m/z 474 ($\text{M}+\text{H}$) with a purity of 98%.

[000161] Compound 32: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(3'-methoxy biphenyl-4-yl)acetamide.



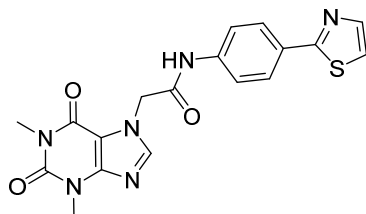
^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.52 (s, 1H), 8.08 (s, 1H), 7.65 (s, 4H), 7.35 (t, $J=8$ Hz, 1H), 7.21 (d, $J=8$ Hz, 1H), 7.16 (m, 1H), 6.91 - 6.88 (m, 1H), 5.22 (s, 2H), 3.81 (s, 3H), 3.20 (s, 3H). LC-MS: m/z 420 ($M+H$) with a purity of 99%.

[000162] Compound 33: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(2-methyl thiazol-4-yl)phenyl)acetamide.



^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.51 (s, 1H), 8.08 (s, 1H), 7.89 (d, $J = 8.8$ Hz, 2H), 7.81 (s, 1H), 7.63 (d, $J = 8.8$ Hz, 2H), 5.22 (s, 2H), 3.46 (s, 3H), 3.20 (s, 3H), 2.70 (s, 3H). LC-MS: m/z 411.5 ($M+H$) with a purity of 96%.

[000163] Compound 34: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiazol-2-yl) phenyl)acetamide.

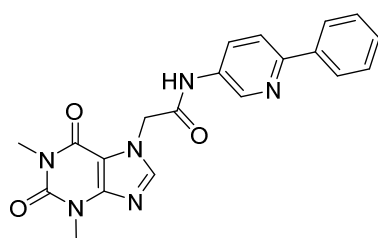


^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.67 (s, 1H), 8.08 (s, 1H), 7.94 - 7.91 (m, 2H), 7.88 (d, $J=3.2$ Hz, 1H), 7.73 - 7.72 (m, 2H), 7.70 (m, 1H), 5.24 (s, 2H), 3.47 (s, 3H), 3.20 (s, 3H). LC-MS: m/z 397 ($M+H$) with a purity of 95%.

[000164] Amide coupling Method E: A solution of commercially available 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetic acid, 1 (1.3 equiv.) and triethylamine (2.1 equiv.) in dichloromethane (0.1 M) was cooled to 0°C under nitrogen atmosphere and treated with

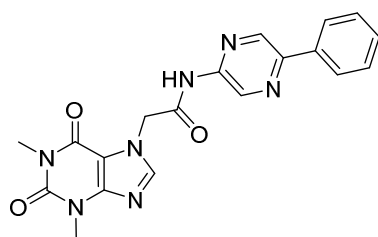
isobutyl chloroformate (2.0 equiv.). The reaction mixture stirred for 30 minutes, treated with the respective amine (1.0 equiv.) and gently brought up to room temperature for 2 – 18 h until judged complete by LC-MS. It was partitioned between dichloromethane and saturated sodium bicarbonate. The organic phase was separated, washed with aqueous sodium chloride, dried over sodium sulfate and concentrated to dryness. The residue was purified using preparative HPLC to give the product.

[000165] Compound 35: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(6-phenylpyridin-3-yl)acetamide.



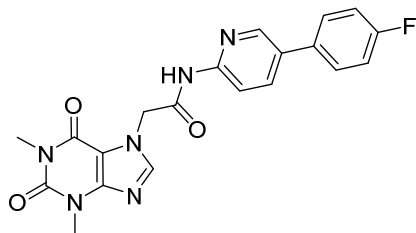
^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.74 (s, 1H), 8.81 – 8.82 (m, 1H), 8.09 – 8.12 (m, 2H), 8.03 – 8.05 (m, 2H), 7.94 – 7.96 (m, 1H), 7.45 – 7.49 (m, 2H), 7.39 – 7.41 (m, 1H), 5.26 (s, 2H), 3.46 (s, 3H), 3.20 (s, 3H). LC-MS: m/z 391 ($M+H$) with a purity of 96%.

[000166] Compound 36: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(5-phenylpyrazin-2-yl)acetamide.



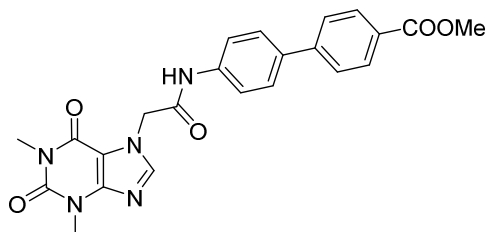
^1H NMR (400 MHz, MeOD- d_4) δ (ppm): 9.35 (bs, 1H), 8.86 (d, $J = 1.2$ Hz, 1H), 8.00 – 8.02 (m, 3H), 7.42 – 7.52 (m, 3H), 5.37 (s, 2H), 3.58 (s, 3H), 3.33 (s, 3H). LC-MS: m/z 392 ($M+H$) with a purity of 99%.

[000167] Compound 37: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(5-(4-fluoro phenyl)pyridin-2-yl)acetamide.



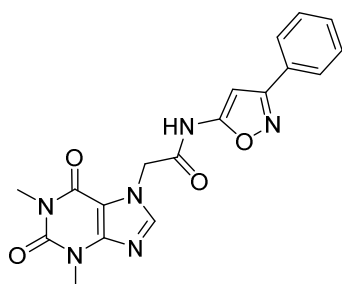
^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 11.08 (bs, 1H), 8.67 (s, 1H), 8.06 – 8.11 (m, 3H), 7.75 – 7.78 (m, 2H), 7.29 – 7.33 (m, 2H), 5.29 (s, 2H), 3.46 (s, 3H), 3.19 (s, 3H). LC-MS: m/z 409 (M+H) with a purity of 98%.

[000168] Compound 38: methyl 4'-(2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamido)biphenyl-4-carboxylate.



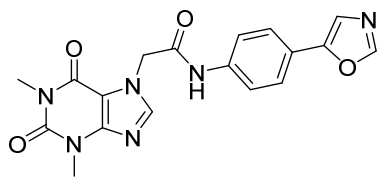
^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.57 (s, 1H), 8.08 (s, 1H), 8.01 (d, J = 8.40 Hz, 2H), 7.81 (d, J = 8.40 Hz, 2H), 7.69 – 7.76 (m, 4H), 5.23 (s, 2H), 3.86 (s, 3H), 3.46 (s, 3H), 3.20 (s, 3H). LC-MS: m/z 448 (M+H) with a purity of 97%.

[000169] Compound 39: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(3-phenyl isoxazol-5-yl)acetamide.



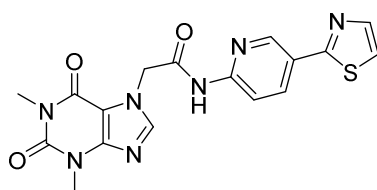
^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 12.28 (s, 1H), 8.08 (s, 1H), 7.82 (s, 2H), 7.49 (s, 3H), 6.68 (s, 1H), 5.29 (s, 2H), 3.46 (s, 3H), 3.19 (s, 3H). LC-MS: m/z 381 (M+H) with a purity of 97%.

[000170] Compound 40: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(oxazol-5-yl) phenyl)acetamide.



^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.59 (s, 1H), 8.39 (s, 1H), 8.07 (s, 1H), 7.68 (m, 4H), 7.59 (s, 1H), 5.22 (s, 2H), 3.46 (s, 3H), 3.20 (s, 3H). LC-MS: m/z 381 (M+H) with a purity of 95%.

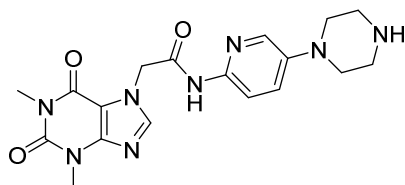
[000171] Compound 41: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(5-(thiazol-2-yl)pyridin-2-yl)acetamide.



^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 11.27 (s, 1H), 8.93 (d, $J=2$ Hz, 1H), 8.32 (dd, $J=8.8$, 2.4 Hz, 1H), 8.11 - 8.09 (m, 1H), 8.07 (s, 1H), 7.95 (d, $J=3.2$ Hz, 1H), 7.82 (d, $J=3.2$ Hz, 1H), 5.31 (s, 2H), 3.46 (s, 3H), 3.19 (s, 3H). LC-MS: m/z 398 (M+H) with a purity of 96%.

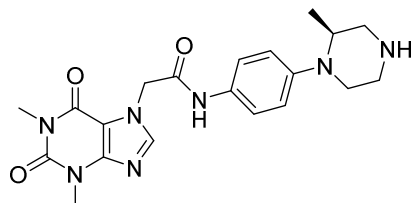
[000172] Removal of Boc protecting group: To a mixture of tert-butyl 4-(6-(2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamido)pyridin-3-yl)piperazine-1-carboxylate, 1 (1 equiv.) in dichloromethane (0.1 M) was added trifluoroacetic acid (10 equiv.) at room temperature. The reaction mixture was allowed to stir for 2 h followed by which the volatiles were evaporated. The resulting mass was then subjected to purification on a preparative TLC.

[000173] Compound 42: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(5-(piperazin-1-yl)pyridin-2-yl)acetamide.



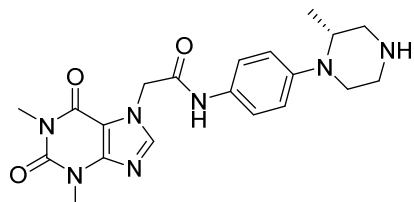
^1H NMR (600 MHz, CDCl_3 : MeOD (10:1)) δ (ppm): 7.86 (d, $J = 8.9$ Hz, 1H), 7.83 (d, $J = 2.8$ Hz, 1H), 7.69 (s, 1H), 7.20 - 7.16 (m, 1H), 5.06 (s, 2H), 3.47 (s, 3H), 3.25 (s, 3H), 3.22 (dt, $J = 3.9$, 1.6 Hz, 1H), 3.14 (dd, $J = 6.2$, 3.9 Hz, 3H), 3.07 - 3.03 (m, 4H). LC-MS: m/z 399 (M + H) with a purity of 96%.

[000174] Compound 43: (S)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(2-methyl piperazin-1-yl)phenyl)acetamide.



^1H NMR (400 MHz, CDCl_3) δ (ppm): 9.37 (s, 1H), 7.77 (s, 1H), 7.45 (d, $J = 8.8$ Hz, 2H), 6.92 (d, $J = 8.8$ Hz, 2H), 4.95 (s, 2H), 3.61 (m, 4H), 3.47 (s, 3H), 3.24 - 3.06 (m, 5H), 2.91 - 2.87 (m, 1H), 0.99 (d, $J = 6.4$ Hz, 3H). LC-MS: m/z 412 ($\text{M}+\text{H}$) with a purity of 99%.

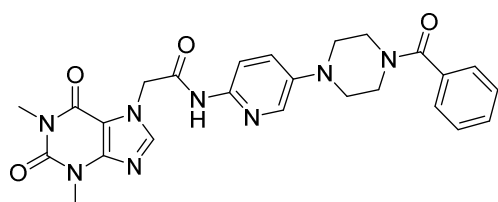
[000175] Compound 44: (R)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(2-methyl piperazin-1-yl)phenyl)acetamide.



^1H NMR (400 MHz, CDCl_3) δ (ppm): 9.37 (s, 1H), 7.77 (s, 1H), 7.45 (d, $J = 8.8$ Hz, 2H), 6.92 (d, $J = 8.8$ Hz, 2H), 4.95 (s, 2H), 3.61 (m, 4H), 3.47 (s, 3H), 3.24 - 3.06 (m, 5H), 2.91 - 2.87 (m, 1H), 0.99 (d, $J = 6.4$ Hz, 3H). LC-MS: m/z 412 ($\text{M}+\text{H}$) with a purity of 99%.

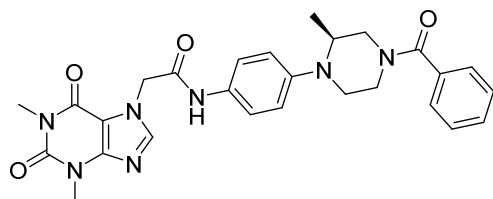
[000176] Acylation Method A: To a solution of 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(5-(piperazin-1-yl)pyridin-2-yl)acetamide, 1 (1 equiv.) in dry N,N-dimethylformamide (0.07 M) was added Hunig's base (2 equiv.) and the respective acid chloride (1 equiv.). The reaction was stirred for 16 h at room temperature then quenched by the addition of distilled water. The solvent was removed in vacuo, and the crude material was partitioned between chloroform and saturated NaHCO_3 . The crude product was further purified by column chromatography.

[000177] Compound 45: N-(5-(4-benzoylpiperazin-1-yl)pyridin-2-yl)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamide.



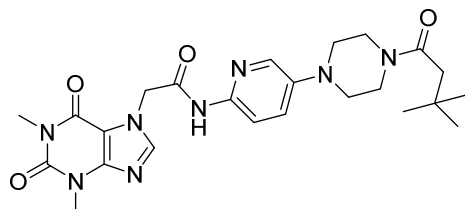
^1H NMR (600 MHz, CDCl_3) δ (ppm): 9.53 (s, 1H), 8.02 (d, J = 8.9 Hz, 1H), 7.98 (d, J = 1.9 Hz, 1H), 7.73 (s, 1H), 7.43 (s, 5H), 7.27 (dd, J = 9.1, 3.0 Hz, 1H), 5.11 (s, 2H), 3.93 (br s, 2H), 3.60 (m, 5H), 3.41 (s, 3H), 3.16 (br d, J = 59.6 Hz, 4H). LC-MS: 503 (M + H), 524 (M+Na) with a purity of 92%.

[000178] Compound 46: (S)-N-(4-(4-benzoyl-2-methylpiperazin-1-yl)phenyl)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamide.



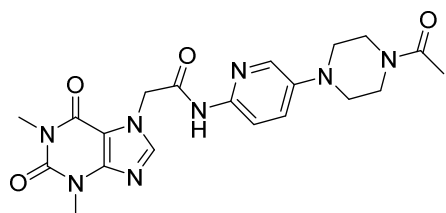
^1H NMR (400 MHz, CDCl_3) δ (ppm): 9.31 (s, 1H), 7.76 (s, 1H), 7.44 - 7.42 (m, 7H), 6.87 (d, J = 8.8 Hz, 2H), 4.94 (s, 2H), 3.61 (m, 4H), 3.46 (m, 5H), 1.55 (s, 7H). LC-MS: m/z 516 (M+H) with a purity of 98%.

[000179] Compound 47: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(5-(4-(3,3-dimethylbutanoyl)piperazin-1-yl)pyridin-2-yl)acetamide.



^1H NMR (600 MHz, C_6D_6) δ (ppm): δ 9.97 (s, 1H), 8.44 (d, J = 9.1 Hz, 1H), 7.94 (d, J = 2.9 Hz, 1H), 7.09 (s, 1H), 6.71 (dd, J = 9.1, 3.0 Hz, 1H), 4.49 (s, 2H), 3.55 (s, 2H), 3.29 (s, 3H), 3.27 (s, 3H), 2.89 (s, 2H), 2.45 (d, J = 39.6 Hz, 4H), 2.03 (s, 2H), 1.10 (s, 9H). LC-MS: m/z 497 (M+H), 495 (M-H) with a purity of 97%.

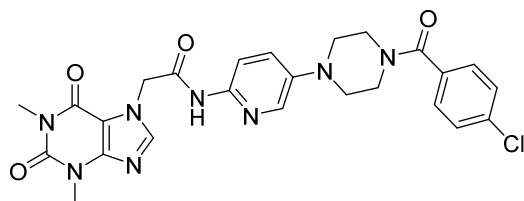
[000180] Compound 48: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(5-(piperazin-1-yl)pyridin-2-yl)acetamide.



^1H NMR (600 MHz, C_6D_6) δ (ppm): δ 9.50 (s, 1H), 8.47 (d, J = 9.2 Hz, 1H), 7.88 (d, J = 2.6 Hz, 1H), 6.86 (s, 1H), 6.66 (dd, J = 9.1, 3.0 Hz, 1H), 4.12 (s, 2H), 3.47 - 3.42 (m, 2H), 3.23 (s, 6H),

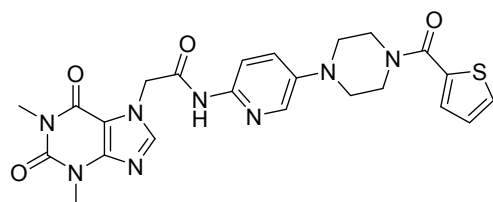
3.01 (s, 3H), 2.66 – 2.59 (m, 2H), 2.39 – 2.34 (m, 2H), 2.25 – 2.21 (m, 2H). LC-MS: m/z 439 (M - H), 441 (M+H) with a purity of 97%.

[000181] Compound 49: N-(5-(4-(4-chlorobenzoyl)piperazin-1-yl)pyridin-2-yl)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamide.



¹H NMR (600 MHz, CDCl₃) δ (ppm): 9.53 (s, 1H), 8.03 (d, J = 9.0 Hz, 1H), 7.97 (d, J = 2.9 Hz, 1H), 7.73 (s, 1H), 7.40 (m, J = 8.7 Hz, 4H), 7.28 – 7.26 (m, 1H), 5.11 (s, 2H), 3.91 (s, 2H), 3.60 (s, 4H), 3.48 (s, 1H), 3.41 (s, 3H), 3.17 (bs, 4H). LC-MS: m/z 537 (M+1) and 535 (M-1) with a purity of 98%.

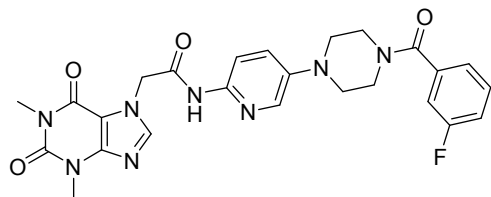
[000182] Compound 50: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(5-(4-(thiophene-2-carbonyl)piperazin-1-yl)pyridin-2-yl)acetamide.



¹H NMR (600 MHz, DMSO-d₆) δ (ppm): 10.77 (s, 1H), 8.07 (d, J = 3.0 Hz, 1H), 8.06 (s, 1H), 7.86 (d, J = 9.0 Hz, 1H), 7.78 (dd, J = 5.0, 1.1 Hz, 1H), 7.46 (dd, J = 3.6, 1.0 Hz, 1H), 7.44 (dd, J = 9.1, 2.9 Hz, 1H), 7.15 (dd, J = 5.0, 3.6 Hz, 1H), 5.22 (s, 2H), 3.79 (m, 4H), 3.45 (s, 3H), 3.22 (m, 4H), 3.19 (s, 3H). LC-MS: m/z 509 (M + H), 507 (M-H) with a purity of 99%.

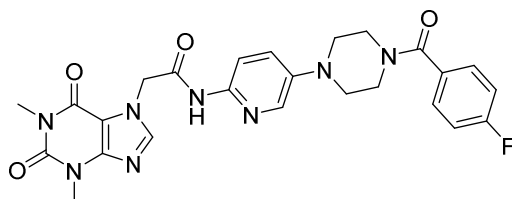
[000183] Acylation Method B: To a mixture of the 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(5-(piperazin-1-yl)pyridin-2-yl)acetamide, 1 (1 equiv.) and the respective acid (1 equiv.) in N,N-dimethylformamide (0.06 M), HATU (1.2 equiv.) and Hunig's base (3 equiv.) in a dropwise fashion at room temperature. The reaction mixture was allowed to stir for 30 min followed by which it was quenched with saturated NaHCO₃ solution. The resulting mixture was extracted with ethyl acetate twice and the combined organic layer was evaporated and the crude products were subjected to purification on a preparative TLC plate.

[000184] Compound 51: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(5-(4-(3-fluoro benzoyl)piperazin-1-yl)pyridin-2-yl)acetamide.



^1H NMR (600 MHz, DMSO- d_6) δ (ppm): 10.80 (s, 1H), 8.09 – 8.02 (m, 2H), 7.85 (d, J = 9.1 Hz, 1H), 7.52 (td, J = 7.9, 5.8 Hz, 1H), 7.43 (dd, J = 9.1, 3.0 Hz, 1H), 7.36 – 7.22 (m, 3H), 5.21 (s, 2H), 3.76 (bs, 2H), 3.45 (s, 3H), 3.24 (bs, 2H), 3.18 (s, 3H), 3.13 (bs, 2H). LC-MS: m/z 521 (M + 1), 519 (M -1) with a purity of 95%.

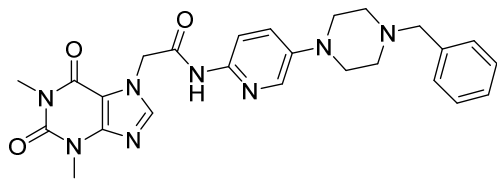
[000185] Compound 52: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(5-(4-(4-fluoro benzoyl)piperazin-1-yl)pyridin-2-yl)acetamide.



^1H NMR (600 MHz, CDCl_3) δ (ppm): 9.69 (s, 1H), 8.04 (d, J = 9.1 Hz, 1H), 7.96 (d, J = 2.8 Hz, 1H), 7.74 (s, 1H), 7.50 – 7.40 (m, 2H), 7.30 (dd, J = 9.2, 3.0 Hz, 1H), 7.15 – 7.08 (m, 2H), 5.12 (s, 2H), 3.90 (bs, 3H), 3.66 (bs, 1H), 3.60 (s, 3H), 3.41 (s, 3H), 3.17 (s, 4H). LC-MS: m/z 519 (M -H) and purity of 98%.

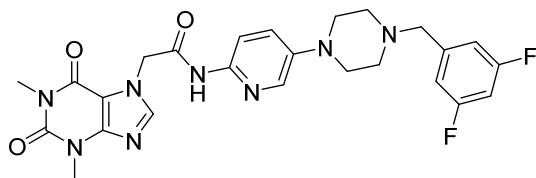
[000186] Alkylation Procedure: To a mixture of the 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(5-(piperazin-1-yl)pyridin-2-yl)acetamide, 1 (1 equiv.) in N,N -dimethylformamide (0.08 M) and Hunig's base was added the respective arylbromide (1 equiv.) at room temperature. The reaction mixture was allowed to stir for 24 h followed by evaporation of the volatiles and addition water. The resulting mixture was extracted with ethyl acetate thrice and the organic layer was evaporated and the crude products were subjected to purification on a preparative TLC plate.

[000187] Compound 53: N-(5-(4-benzylpiperazin-1-yl)pyridin-2-yl)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamide.



^1H NMR (600 MHz, CDCl_3) δ (ppm): 9.64 (s, 1H), 8.01 (d, $J = 2.9$ Hz, 1H), 7.99 (d, $J = 9.1$ Hz, 1H), 7.76 (s, 1H), 7.37 (m, 5H), 7.33 (d, $J = 4.3$ Hz, 1H), 5.10 (s, 2H), 3.59 (s, 3H), 3.57 (s, 2H), 3.40 (s, 3H), 3.22 – 3.13 (m, 4H), 2.71 – 2.45 (m, 4H). LC-MS: 489 ($M + H$) with a purity of 94%.

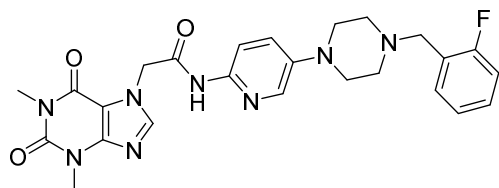
[000188] Compound 54: N-(5-(4-(3,5-difluorobenzyl)piperazin-1-yl)pyridin-2-yl)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamide.



^1H NMR (600 MHz, CDCl_3) δ (ppm): 9.33 (s, 1H), 8.02 – 7.94 (m, 2H), 7.73 (d, $J = 13.6$ Hz, 1H), 7.25 – 7.22 (m, 1H), 6.90 (t, $J = 13.6$ Hz, 2H), 6.74 – 6.65 (m, 1H), 5.13 – 5.04 (m, 2H), 3.63 – 3.59 (m, 3H), 3.57 – 3.52 (m, 2H), 3.45 – 3.39 (m, 3H), 3.18 (dd, $J = 14.6, 9.6$ Hz, 4H), 2.62 (s, 4H). LC-MS: m/z 525 ($M+H$), 523 ($M-H$) with purity of 97%.

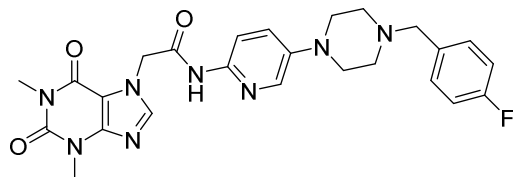
[000189] Reductive amination procedure: To a mixture of the 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(5-(piperazin-1-yl)pyridin-2-yl)acetamide, 1 (1 equiv.) and the respective aldehyde (1 equiv.) in dichloroethane (0.1 M) was added acetic acid (2 equiv.) followed by triacetoxy sodium borohydride (1.4 equiv.) at room temperature. The reaction was stirred for an hour and then quenched with saturated NaHCO_3 (1 mL). The organics were extracted in ethyl acetate trice and the combined organic layers were dried. The residue was purified by using preparative TLC.

[000190] Compound 55: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(5-(4-(2-fluorobenzyl)piperazin-1-yl)pyridin-2-yl)acetamide.



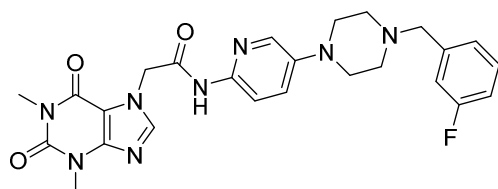
^1H NMR (600 MHz, CDCl_3) δ (ppm): 9.61 (s, 1H), 7.99 – 7.98 (m, 1H), 7.96 (d, $J = 9.2$ Hz, 1H), 7.73 (s, 1H), 7.45 – 7.38 (m, 1H), 7.29 – 7.24 (m, 1H), 7.22 (dd, $J = 9.1, 3.0$ Hz, 1H), 7.15 – 7.10 (m, 1H), 7.07 – 7.02 (m, 1H), 5.10 (s, 2H), 3.67 (s, 2H), 3.59 (s, 3H), 3.40 (s, 3H), 3.24 – 3.13 (m, 4H), 2.67 (s, 4H). LC-MS: m/z 507 ($M + 1$), 505($M-1$) with purity of 96%.

[000191] Compound 56: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(5-(4-fluorobenzyl)piperazin-1-yl)pyridin-2-yl)acetamide.



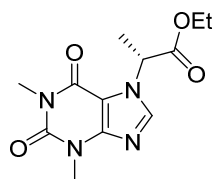
^1H NMR (600 MHz, CDCl_3) δ (ppm): 9.29 (s, 1H), 7.98 (d, $J = 9.1$ Hz, 1H), 7.95 (d, $J = 2.4$ Hz, 1H), 7.73 (s, 1H), 7.38 (m, 2H), 7.26 – 7.20 (m, 1H), 7.04 (t, $J = 8.6$ Hz, 2H), 5.08 (s, 2H), 3.64 (bs, 2H), 3.60 (s, 3H), 3.42 (s, 3H), 3.25 (bs, 4H), 2.70 (bs, 4H). LC-MS: m/z 507 ($M + 1$), 505($M-1$) with a purity of 96%.

[000192] Compound 57: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(5-(3-fluorobenzyl)piperazin-1-yl)pyridin-2-yl)acetamide.



^1H NMR (600 MHz, CDCl_3) δ (ppm): 9.48 (s, 1H), 8.01 (s, 1H), 7.99 (m, 1H), 7.76 (s, 1H), 7.34 – 7.29 (m, 1H), 7.28 – 7.23 (m, 1H), 7.15 – 7.09 (m, 2H), 6.99 (ddd, $J = 7.8, 5.2, 1.8$ Hz, 1H), 5.12 (s, 2H), 3.65 – 3.61 (m, 3H), 3.62 – 3.58 (m, 2H), 3.44 (s, 3H), 3.25 – 3.16 (m, 4H), 2.66 (m, 4H). LC-MS: m/z 507 ($M + H$), 505 ($M-H$) with a purity of 95%.

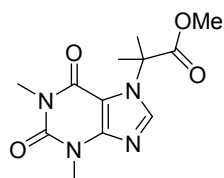
[000193] Mitsunobu reaction conditions:



To a stirred solution of commercially available 1,3-dimethyl-1H-purine-2,6(3H,7H)-dione, **1** (2 equiv.), (S)-ethyl 2-hydroxypropanoate, **2** (1 equiv.) and triphenyl phosphine (1.45 g, 5.555) in tetrahydrofuran (0.14 M) was added DIAD (2 equiv.) dropwise at room temperature, and the

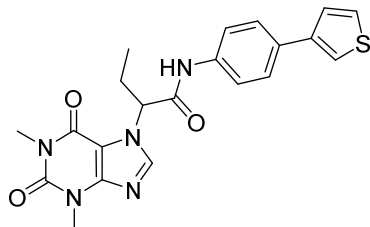
resulting reaction mixture was stirred for 5 h. After completion of starting material, the reaction mixture was diluted with water and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated under vacuum. The crude compound was purified by column chromatography to afford the product.

[000194] Alkylation Method A:



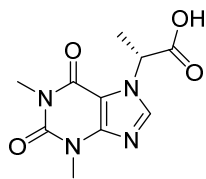
To a solution of commercially available 1,3-dimethyl-1H-purine-2,6(3H,7H)-dione, 1 (1 equiv.) in N,N-dimethylformamide (0.28 M) was added methyl 2-bromo-2-methylpropanoate, 2 (1.2 equiv.), K_2CO_3 (2 equiv.) at room temperature and warmed to 80°C for 20 h. After completion, the reaction mixture was cooled to room temperature; water was added and mixture was extracted with ethyl acetate trice. The combined ethyl acetate layers were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, rotary evaporated and dried under vacuum to afford the product.

[000195] Alkylation Method B:



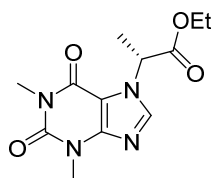
A solution of 1,3-dimethyl-1H-purine-2,6(3H,7H)-dione, 2 (1 equiv.) and 2-bromo-N-(4-(thiophen-3-yl)phenyl)butanamide, 1 (1.1 equiv.) in N,N-dimethylformamide (0.1 M) cooled to 0°C under nitrogen atmosphere, was treated with sodium hydride (2.5 equiv., 60% mineral oil). The mixture was stirred for 18 h at room temperature under nitrogen atmosphere and was partitioned between dichloromethane and water. The organic phase was separated, washed with aqueous sodium chloride, dried over sodium sulfate and concentrated to dryness. The residue was purified using preparative HPLC to give the final product.

[000196] Hydrolysis Conditions:



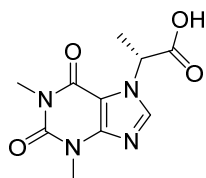
To a stirred solution of (R)-ethyl 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanoate, 3 (1 equiv.) in tetrahydrofuran (0.18 M), methanol (0.36 M) and water (0.36 M) was added LiOH.H₂O (1.5 equiv.) at room temperature and resulting reaction mixture was stirred at room temperature for 2 h. After completion of starting material, the reaction mixture was concentrated and the residue was dissolved in water and washed with ethyl acetate twice and acidified with aq.KHSO₄; product was extracted with 10% methanol/chloroform twice. The combined organic layers were dried using Na₂SO₄, concentrated under vacuum to give the product.

[000197] Compound 58 (R)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl)propanamide.



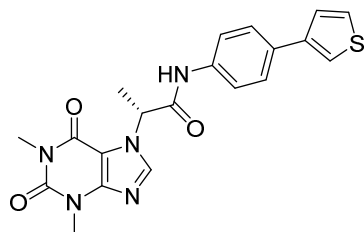
Step 1: Preparation of (R)-ethyl 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanoate.

Intermediate was prepared using the Mitsunobu conditions as described. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.75 (s, 1H), 5.63-5.58(q, J=6.8 Hz, 1H), 4.26-4.24 (q, J=6.8 Hz, 2H), 3.61 (s, 3H), 3.39 (s, 3H), 1.86-1.84 (d, J=6.8 Hz, 3H), 1.29-1.25 (t, J=6.8 Hz, 3H). LC-MS: m/z 281.3(M+H) with a purity of 43%.



Step 2: Preparation of (R)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl) propanoic acid.

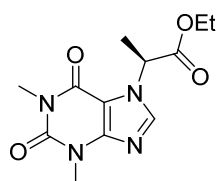
Intermediate was prepared using the hydrolysis condition as described. ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 13.25 (brs, 1H), 8.20 (s, 1H), 5.50-5.44 (q, J=7.6 Hz, 1H), 3.44 (s, 3H), 3.24 (s, 3H), 1.76-1.74(d, J=7.6 Hz, 3H). LC-MS: m/z 250.9(M+H) with a purity of 97 %.



Step 3: Preparation of (R)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl)propanamide.

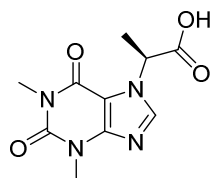
The final product was prepared using amide coupling method A reaction conditions as described. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.47 (s, 1H), 8.33 (s, 1H), 7.79 (s, 1H), 7.69-7.67 (d, J = 8.8 Hz, 2H), 7.62-7.60 (d, J = 8.4 Hz, 3H), 7.53-7.52 (d, J = 4.8 Hz, 1H), 5.71-5.69 (q, J = 6.9 Hz, 1H), 3.46 (s, 3H), 3.20 (s, 3H), 1.84-1.83 (d, J = 6.8 Hz, 3H). LC-MS: m/z 410.13 (M+H) with a purity of 99%.

[000198] Compound 59: (S)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl)propanamide.



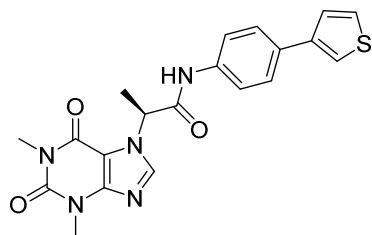
Step 1: Preparation of (S)-ethyl 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanoate.

Intermediate was prepared using the Mitsunobu conditions as described. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.75 (s, 1H), 5.63-5.58 (q, J =6.8 Hz, 1H), 4.26-4.24 (q, J =6.8 Hz, 2H), 3.61 (s, 3H), 3.39 (s, 3H), 1.86-1.84 (d, J =6.8 Hz, 3H), 1.29-1.25 (t, J =6.8 Hz, 3H). LC-MS: m/z 281.4 (M+H) with a purity of 32%.



Step 2: Preparation of (S)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanoic acid.

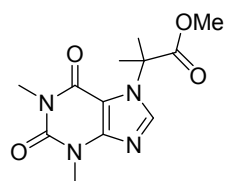
Intermediate was prepared using the hydrolysis condition as described. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 13.25 (brs, 1H), 8.20 (s, 1H), 5.50-5.44 (q, J =7.6 Hz, 1H), 3.44 (s, 3H), 3.24 (s, 3H), 1.76-1.74 (d, J =7.6 Hz, 3H). LC-MS: m/z 226.14 (M+H) with a purity of 95%.



Step 3: (S)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl)propanamide.

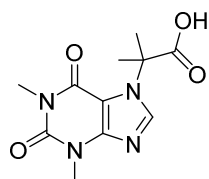
The final product was prepared using amide coupling method A reaction conditions as described. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.47 (s, 1H), 8.33 (s, 1H), 7.79 (s, 1H), 7.69-7.67 (d, J = 8.8 Hz, 2H), 7.62-7.60 (d, J = 8.4 Hz, 3H), 7.53-7.52 (d, J = 4.8 Hz, 1H), 5.71-5.69 (q, J = 6.9 Hz, 1H), 3.46 (s, 3H), 3.20 (s, 3H), 1.84-1.83 (d, J = 6.8 Hz, 2H). LC-MS: m/z 410.07 (M+H) with a purity of 99%. ee: 99.67%.

[000199] Compound 60: (S)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl)propanamide.



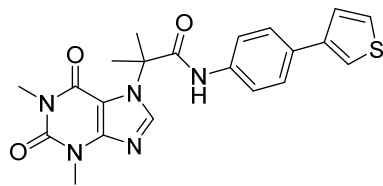
Step 1: Preparation of methyl 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-2-methylpropanoate.

Intermediate was prepared using alkylation method A conditions as described. ^1H -NMR (400 MHz; DMSO- d_6) δ (ppm): 8.24 (s, 1H), 3.62 (s, 3H), 3.44 (s, 3H), 3.19 (s, 3H), 1.80 (s, 6H). MS (ESI): m/z 281 [M+H] $^+$. LC-MS: Purity of 34%.



Step 2: Preparation of 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-2-methylpropanoic acid.

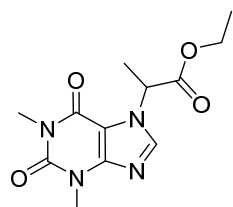
Intermediate was prepared using hydrolysis conditions as described. ^1H -NMR (400 MHz; DMSO- d_6) δ (ppm): 13.10 (brs, 1H), 8.22 (s, 1H), 3.45 (s, 3H), 3.21 (s, 3H), 1.81 (s, 6H). MS (ESI): m/z 267 [M+H] $^+$. LC-MS: Purity of 87%.



Step 3: Preparation of 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-2-methyl-N-(4-(thiophen-3-yl)phenyl)propanamide.

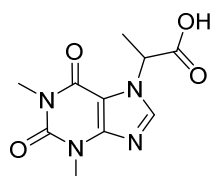
[000200] The final product was prepared using amide coupling method A reaction conditions as described. ^1H -NMR (400 MHz; DMSO- d_6) δ (ppm): 9.37 (s, 1H), 8.28 (s, 1H), 7.78 (s, 1H), 7.65-7.60 (m, 3H), 7.60-7.52 (m, 3H), 3.47 (s, 3H), 3.17 (s, 3H), 1.90 (s, 6H). MS (ESI): m/z 424.05 $[\text{M}^+ \text{H}]^+$. LC-MS: Purity of 96%.

[000201] Compound 61: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl) phenyl)propanamide.



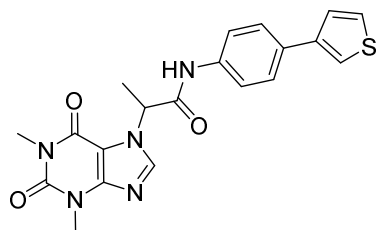
Step 1: Preparation ethyl 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanoate.

Intermediate was prepared using alkylation method A conditions as described. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.97 (s, 1H), 5.59 (q, $J = 7.60$ Hz, 1H), 4.24 (q, $J = 7.20$ Hz, 2H), 3.58 (s, 3H), 3.36 (s, 3H), 1.83 (d, $J = 7.60$ Hz, 3H), 1.28 (t, $J = 7.20$ Hz, 3H). LC-MS: m/z 281 (M+H).



Step 2: Preparation 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanoic acid.

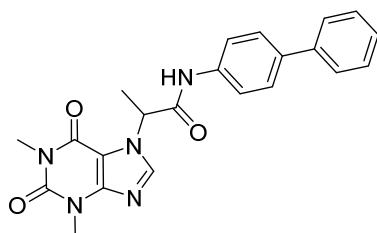
Intermediate was prepared using hydrolysis conditions as described. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.19 (s, 1H), 5.46 (q, $J = 7.20$ Hz, 1H), 3.44 (s, 3H), 3.21 (s, 3H), 1.74 (d, $J = 7.20$ Hz, 3H). LC-MS: m/z 253 (M+H).



Step 3: Preparation 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl)propanamide.

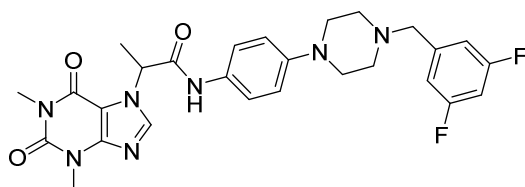
The final product was prepared using amide coupling method D reaction conditions as described. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.46 (s, 1H), 8.31 (s, 1H), 7.78 (d, J = 1.60 Hz, 1H), 7.60 – 7.68 (m, 5H), 7.52 (d, J = 4.80 Hz, 1H), 5.69 (q, J = 7.20 Hz, 1H), 3.45 (s, 3H), 3.20 (s, 3H), 1.83 (d, J = 7.20 Hz, 1H). LC-MS: m/z 410 ($M+H$) with a purity of 97%.

[000202] Compound 62: N-(biphenyl-4-yl)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanamide.



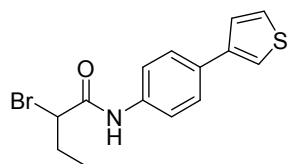
The final product was prepared using amide coupling method D reaction conditions as described. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.49 (s, 1H), 8.32 (s, 1H), 7.62 – 7.68 (m, 6H), 7.43 (t, J = 7.60 Hz, 2H), 7.32 (t, J = 7.60 Hz, 1H), 5.70 (q, J = 7.20 Hz, 1H), 3.46 (s, 3H), 3.20 (s, 3H), 1.84 (d, J = 7.20 Hz, 3H). LC-MS: m/z 404 ($M+H$) with a purity of 99%.

[000203] Compound 63: N-(4-(4-(3,5-difluorobenzyl)piperazin-1-yl)phenyl)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanamide.



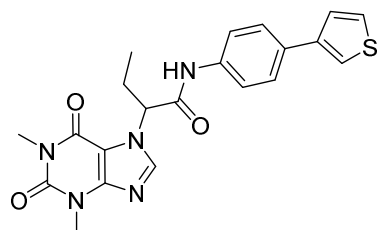
Product was prepared using alkylation method A reaction conditions as described. ^1H NMR (600 MHz, CDCl_3) δ (ppm): 9.25 (s, 1H), 7.86 (s, 1H), 7.42 (d, J = 9.1 Hz, 2H), 6.92 (d, J = 6.3 Hz, 2H), 6.85 (d, J = 9.1 Hz, 2H), 6.70 (m, 1H), 5.55 (q, J = 7.1 Hz, 1H), 3.60 (s, 3H), 3.56 (s, 2H), 3.46 (s, 3H), 3.17 (m, 4H), 2.62 (m, 4H), 1.87 (d, J = 7.1 Hz, 3H). LC-MS: m/z 538 ($M + 1$) with HPLC purity of 99%.

[000204] Compound 64: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl)butanamide.



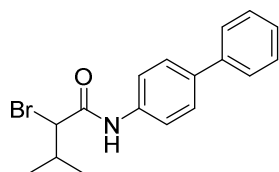
Step 1: Preparation 2-bromo-N-(4-(thiophen-3-yl)phenyl)butanamide.

Intermediate was prepared using amide coupling method E reaction conditions as described. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.58 – 7.59 (m, 4H), 7.42 (s, 1H), 7.36 – 7.40 (m, 2H), 4.43 – 4.48 (m, 1H), 2.22 – 2.31 (m, 1H), 2.07 – 2.20 (m, 1H), 1.10 – 1.14 (m, 3H).



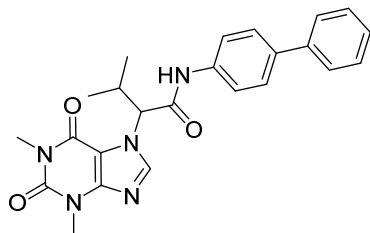
Step 2: Preparation 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl)butanamide. Final product was prepared using the alkylation method B reaction conditions as described. ^1H NMR (400 MHz, MeOD-d_4) δ (ppm): 8.26 (s, 1H), 7.61 (s, 4H), 7.56 – 7.57 (m, 1H), 7.42 – 7.46 (m, 2H), 5.67 – 5.71 (m, 1H), 3.56 (s, 3H), 3.36 (s, 3H), 2.23 – 2.38 (m, 2H), 1.04 – 1.07 (m, 3H). LC-MS: m/z 424 ($\text{M}+\text{H}$) with a purity of 97%.

[000205] Compound 65: N-(biphenyl-4-yl)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-3-methylbutanamide.



Step 1: Preparation N-(biphenyl-4-yl)-2-bromo-3-methylbutanamide.

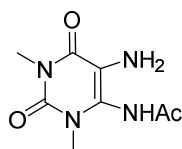
Intermediate was prepared using amide coupling method B reaction conditions as described. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.40 (s, 1H), 7.63 – 7.70 (m, 6H), 7.42 – 7.46 (m, 2H), 7.31 – 7.35 (m, 1H), 4.30 – 4.33 (m, 1H), 2.19 – 2.28 (m, 1H), 1.11 (d, $J = 6.80$ Hz, 3H), 0.99 (d, $J = 6.80$ Hz, 3H). LC-MS: m/z 404 ($\text{M}+\text{H}$).



Step 2: Preparation N-(biphenyl-4-yl)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-3-methylbutanamide.

The product was prepared using alkylation method A reaction conditions as described. ^1H NMR (400 MHz, MeOD- d_4) δ (ppm): 8.36 (s, 1H), 7.66 – 7.69 (m, 2H), 7.58 – 7.60 (m, 4H), 7.41 (t, J = 7.60 Hz, 2H), 7.30 (t, J = 7.60 Hz, 1H), 5.52 – 5.54 (m, 1H), 3.56 (s, 3H), 3.38 (s, 3H), 2.57 – 2.67 (m, 1H), 1.16 (d, J = 6.80 Hz, 3H), 0.96 (d, J = 6.80 Hz, 3H). LC-MS: m/z 432 (M+H) with a purity of 99%.

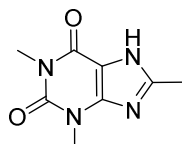
[000206] Preparation of 1,3,8-trimethyl-1H-purine-2,6(3H,7H)-dione.



Step 1: Preparation of N-(5-amino-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)acetamide.

To a stirred solution of commercially available 5,6-diamino-1,3-dimethylpyrimidine-2,4(1H,3H)-dione, 1 (1 equiv.) in acetic acid (4 equiv.) at room temperature and warmed to 70°C for 4 h. The reaction mixture was cooled to room temperature then diluted with ice water and concentrated under reduced pressure to get crude compound, dried under vacuum. The resultant crude was precipitated with 20% dichloromethane in hexane to afford N-(5-amino-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)acetamide as a yellow solid. ^1H -NMR (400 MHz; DMSO- d_6) δ (ppm): 8.36 (s, 1H), 6.58 (s, 2H), 3.30 (s, 3H), 3.10 (s, 3H), 1.92 (s, 3H).

MS (ESI): m/z 213 [M+ H] $^+$. LC-MS: Purity of 96%.

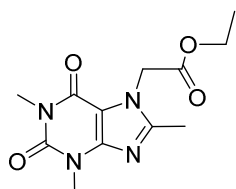


Step 2: Preparation of 1,3,8-trimethyl-1H-purine-2,6(3H,7H)-dione.

To a stirred solid of N-(5-amino-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)acetamide, 2 at room temperature and warmed to 250°C for 2 h. The reaction mixture was cooled to room temperature and the reaction mixture was precipitated with 30%

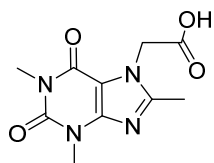
dichloromethane in hexane to afford 1,3,8-trimethyl-1H-purine-2,6(3H,7H)-dione as a yellow solid. $^1\text{H-NMR}$ (400 MHz; DMSO-d_6) δ (ppm): 12.50 (brs, 1H), 3.40 (s, 3H), 3.22 (s, 3H), 2.37 (s, 3H). MS (ESI): m/z 195 $[\text{M} + \text{H}]^+$. LC-MS: Purity of 96%.

[000207] Compound 66: N-(4-(thiophen-3-yl)phenyl)-2-(1,3,8-trimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamide.



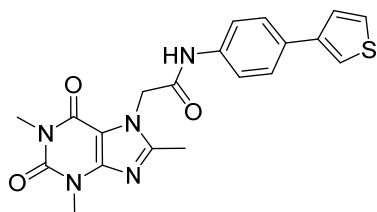
Step 1: Preparation of ethyl 2-(1,3,8-trimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetate.

Intermediate was prepared using alkylation method A reaction conditions as described. $^1\text{H-NMR}$ (400 MHz; CDCl_3) δ (ppm): 5.09 (s, 2H), 4.27 (q, $J = 7.2$ Hz), 3.58 (s, 3H), 3.38 (s, 3H), 2.43 (s, 3H), 1.31 (t, $J = 7.2$ Hz, 3H). MS (ESI): m/z 281 $[\text{M} + \text{H}]^+$. LC-MS: Purity of 93%.



Step 2: Preparation of 2-(1,3,8-trimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetic acid.

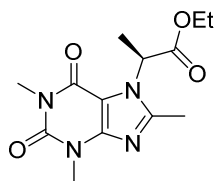
Intermediate was prepared using hydrolysis reaction conditions as described. $^1\text{H-NMR}$ (400 MHz; DMSO-d_6) δ (ppm): 13.34 (brs, 1H), 5.08 (s, 2H), 3.41 (s, 3H), 3.20 (s, 3H), 2.38 (s, 3H). MS (ESI): m/z 251 $[\text{M} - \text{H}]^-$. LC-MS: Purity of 94%.



Step 3: Preparation of N-(4-(thiophen-3-yl)phenyl)-2-(1,3,8-trimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamide.

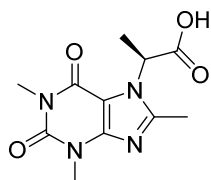
Product was prepared using amide coupling method A reaction conditions as described. $^1\text{H-NMR}$ (400 MHz; DMSO-d_6) δ (ppm): 10.50 (s, 1H), 7.80 (s, 1H), 7.70-7.61 (m, 5H), 7.53 (d, $J = 4.4$ Hz, 1H), 5.22 (s, 2H), 3.44 (s, 3H), 3.20 (s, 3H), 2.42 (s, 3H). MS (ESI): m/z 408.5 $[\text{M} - \text{H}]^-$. LC-MS: Purity of 96%.

[000208] Compound 67: (S)-N-(4-(thiazol-2-yl) phenyl)-2-(1,3,8-trimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanamide.



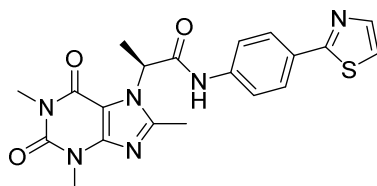
Step 1: Preparation of (S)-ethyl 2-(1,3,8-trimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanoate.

Intermediate was prepared using Mitsunobu reaction conditions as described. $^1\text{H-NMR}$ (400 MHz; CDCl_3) δ (ppm): 5.50 (q, $J = 7.2$ Hz, 1H), 4.11 (q, $J = 3.6$ Hz, 2H), 3.41 (s, 3H), 3.19 (s, 3H), 2.46 (s, 3H), 1.66 (d, $J = 7.2$ Hz, 3H), 1.14 (t, $J = 7.2$ Hz, 3H). LC-MS: m/z 295.1 ($\text{M}+\text{H}$) with a purity of 57.79 % (desired). LCMS: m/z 279 ($\text{M}+\text{H}$) with a purity of 31% .



Step 2: Preparation of (S)-2-(1,3,8-trimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanoic acid.

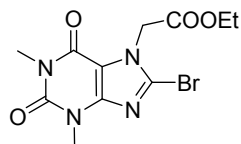
Intermediate was prepared using hydrolysis reaction conditions as described. $^1\text{H-NMR}$ (400 MHz; DMSO-d_6) δ (ppm): 13.03 (brs, 1H), 5.43 (q, $J = 6.8$ Hz, 1H), 3.41 (s, 3H), 3.20 (s, 3H), 2.45 (s, 3H), 1.66 (d, $J = 7.2$ Hz, 3H). LC-MS: m/z 267.1 [$\text{M}+\text{H}$] $^+$. LC-MS: Purity of 98%.



Step 3: Preparation of (S)-N-(4-(thiazol-2-yl) phenyl)-2-(1,3,8-trimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanamide.

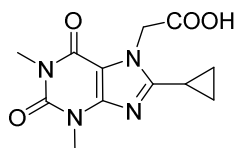
[000209] Product was prepared using amide coupling method A reaction conditions as described. $^1\text{H-NMR}$ (400 MHz; DMSO-d_6) δ (ppm): 9.99 (s, 1H), 7.89-7.82 (m, 3H), 7.71-7.65 (m, 3H), 5.74 (q, $J = 6.9$ Hz, 1H), 3.46 (s, 3H), 3.33 (s, 3H), 3.19 (s, 3H), 1.77 (d, $J = 7.2$ Hz, 3H). LC-MS: m/z 422.9 [$\text{M}-\text{H}$] $^-$ (95%) and 90% ee.

[000210] Preparation of ethyl 2-(8-bromo-1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl) acetate.



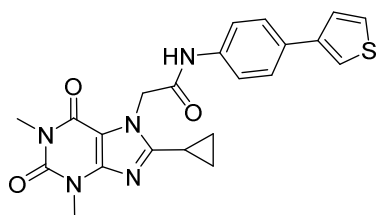
To a solution of commercially available 8-bromo-1,3-dimethyl-1H-purin-2,6(3H,7H)-dione (1 equiv.) in N,N-dimethylformamide (0.2 M) was added bromoethylacetate (1.2 equiv.), K_2CO_3 (2.5 equiv.) at room temperature and warmed to 70°C for 4 h. The reaction mixture was cooled to room temperature then poured into ice water to precipitate the crude compound. The solid was filtered and washed with water, dried under vacuum. The resultant solid was re-crystallized with isopropanol to afford the product. 1H -NMR (400 MHz; $CDCl_3$) δ (ppm): 5.12 (s, 2H), 4.28 (q, J = 7.6 Hz, 2H), 3.58 (s, 3H), 3.38 (s, 3H), 1.32 (t, J = 6.8 Hz, 3H). MS (ESI): m/z 331 $[M+H]^+$.

[000211] Compound 68: N-(4-(thiophen-3-yl)phenyl)-2-(1,3,8-trimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamide.



Step 1: Preparation of 2-(8-cyclopropyl-1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetic acid.

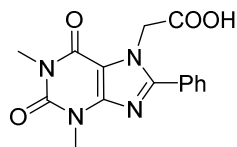
Intermediate was prepared using Suzuki Method C reaction conditions as described. 1H -NMR (400 MHz; $DMSO-d_6$) δ (ppm): 13.30 (brs, 1H), 5.20 (s, 2H), 3.37 (s, 3H), 3.19 (s, 3H), 2.15-2.12 (m, 1H), 1.05 (d, J = 2.8 Hz, 2H), 0.98 (d, J = 2.8 Hz, 2H). MS (ESI): m/z 279 $[M+H]^+$. LC-MS: Purity of 88%.



Step 2: Preparation of 2-(8-cyclopropyl-1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl)acetamide.

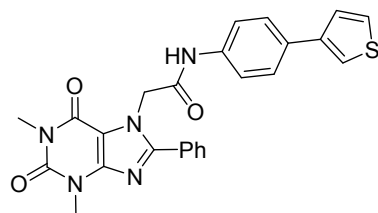
Product was prepared using amide coupling reaction conditions as described. 1H -NMR (400 MHz; $DMSO-d_6$) δ (ppm): 10.46 (s, 1H), 7.78 (s, 1H), 7.69-7.52 (m, 5H), 7.52 (d, J = 4.4 Hz, 1H), 5.32 (s, 2H), 3.39 (s, 3H), 3.19 (s, 3H), 2.15 (m, 1H), 1.06-1.02 (m, 4H). MS (ESI): m/z 436 $[M+H]^+$. LC-MS: Purity of 94%.

[000212] Compound 69: N-(4-(thiophen-3-yl)phenyl)-2-(1,3,8-trimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamide.



Step 1: Preparation of 2-(1,3-dimethyl-2,6-dioxo-8-phenyl-2,3-dihydro-1H-purin-7(6H)-yl)acetic acid.

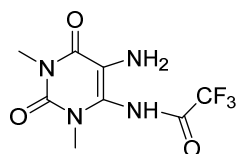
Intermediate was prepared using Suzuki Method C reaction conditions as described. $^1\text{H-NMR}$ (400 MHz; DMSO-d_6) δ (ppm): 13.38 (brs, 1H), 7.67-7.57 (m, 5H), 5.01 (s, 2H), 3.49 (s, 3H), 3.25 (s, 3H). MS (ESI): m/z 315 $[\text{M} + \text{H}]^+$. LC-MS: Purity of 94%.



Step 2: Preparation of 2-(1,3-dimethyl-2,6-dioxo-8-phenyl-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl)acetamide.

Product was prepared using amide coupling reaction conditions as described. $^1\text{H-NMR}$ (400 MHz; DMSO-d_6) δ (ppm): 10.53 (s, 1H), 7.80 (s, 1H), 7.72-7.67 (m, 5H), 7.61-7.53 (m, 6H), 5.21 (s, 2H), 3.51 (s, 3H), 3.24 (s, 3H). MS (ESI): m/z 472 $[\text{M} + \text{H}]^+$. LC-MS: Purity of 98%.

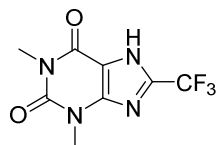
[000213] Compound 70: 2-(1,3-dimethyl-2,6-dioxo-8-(trifluoromethyl)-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl)acetamide.



Step 1: Preparation of N-(5-amino-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-2,2,2-trifluoroacetamide.

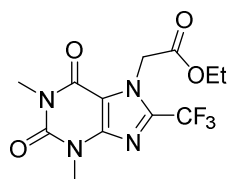
To a stirred solution of commercially available 5,6-diamino-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (1 equiv.) in benzene (0.06 M) at room temperature was added trifluoroacetic acid (1 equiv.) and the resulting reaction mixture was heated to reflux for 4 h. After completion of the starting material, the reaction mixture was cooled to room temperature and concentrated under vacuum. The residue was washed with diethyl ether and dried to give the intermediate N-(5-amino-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-2,2,2-trifluoroacetamide as a

brown solid. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.76 (s, 1H), 6.97 (s, 2H), 3.32 (s, 3H), 3.11 (s, 3H). LC-MS: m/z 264.9 (M-H) with a purity of 84%.



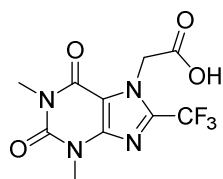
Step 2: Preparation of 1,3-dimethyl-8-(trifluoromethyl)-1H-purine-2,6(3H,7H)-dione.

N-(5-amino-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-2,2,2-trifluoroacetamide was mixed with P_2O_5 (w/w) and heated to 200°C for 15 h. The black mass was cooled to room temperature and quenched with ice and extracted with ethyl acetate twice. The combined ethyl acetate layers were dried over Na_2SO_4 and concentrated under vacuum. The crude compound was purified by column chromatography to afford the intermediate 1,3-dimethyl-8-(trifluoromethyl)-1H-purine-2,6(3H,7H)-dione as a light brown solid. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.34 (s, 3H), 3.26 (brs, 1H), 3.24 (s, 3H). LC-MS: m/z 249.0 (M+H) with a purity of 88%.



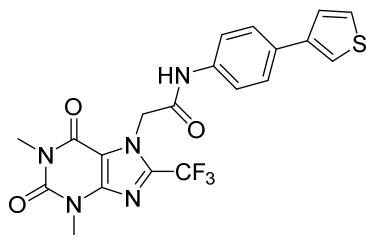
Step 3: Preparation of ethyl 2-(1,3-dimethyl-2,6-dioxo-8-(trifluoromethyl)-2,3-dihydro-1H-purin-7(6H)-yl)acetate.

Intermediate was prepared using alkylation method A reaction conditions as described. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 5.28 (s, 2H), 4.31-4.25 (q, $J=7.2$ Hz, 2H), 3.61 (s, 3H), 3.40 (s, 3H), 1.29-1.21 (t, $J=7.2$ Hz, 3H).



Step 4: Preparation of 2-(1,3-dimethyl-2,6-dioxo-8-(trifluoromethyl)-2,3-dihydro-1H-purin-7(6H)-yl)acetic acid.

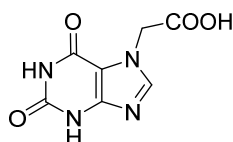
Intermediate was prepared using hydrolysis reaction conditions as described. LC-MS: m/z 307.3(M+H) with a purity of 41%.



Step 5: Preparation of 2-(1,3-dimethyl-2,6-dioxo-8-(trifluoromethyl)-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl)acetamide.

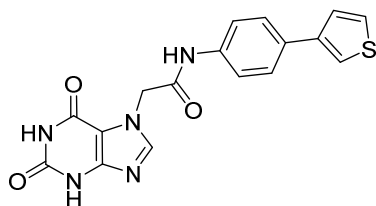
Product was prepared using amide coupling method A reaction conditions as described. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.57 (s, 1H), 7.79-7.70 (m, 1H), 7.68-7.66 (d, $J = 8.4$ Hz, 2H), 7.61-7.55 (m, 3H), 7.52-7.50 (dd, $J_1 = 3.2$ Hz, $J_2 = 1.6$ Hz, 1H), 5.43 (s, 2H), 3.45 (s, 3H), 3.22 (s, 3H). LC-MS: m/z 464.02 ($M+H$) with a purity of 97%.

[000214] Compound 71: 2-(2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl) acetamide.



Step 1: Preparation of 2-(2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetic acid.

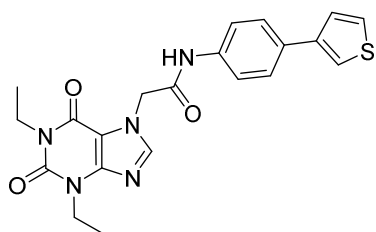
Commercially available 1H-purine-2,6(3H,7H)-dione (1 equiv.) in water (1.5 M) at room temperature was added 2M NaOH solution (0.65 M) and the resulting solution was stirred for 30 min and chloroacetic acid (1 equiv.) was added and resulting reaction mixture was refluxed for 5 h. The reaction mixture was cooled to room temperature and stirred for 16 h. The precipitated solid was removed by filtration and water was acidified with conc HCl (pH 2). The solid collected by filtration, washed with hot ethanol to afford the intermediate 2-(2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetic acid as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 13.35 (brs, 1H), 11.59 (s, 1H), 10.88 (brs, 1H), 7.91(s, 1H), 5.0 (s, 2H). LC-MS: m/z 211.1 ($M+H$) with a purity of 97%.



Step 2: Preparation of 2-(2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl)acetamide.

Product was prepared using amide coupling method D reaction conditions as described. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 11.60 (s, 1H), 10.88 (brs, 1H), 10.43 (brs, 1H), 7.95 (s, 1H), 7.80-7.79 (d, J = 2 Hz, 1H), 7.70-7.67 (d, J = 8.8 Hz, 2H), 7.61-7.59 (m, 3H), 7.53-7.52 (d, J = 4.8 Hz, 1H), 5.14 (s, 2H). LC-MS: m/z 366.10 (M-H) with a purity of 95.43 %. HPLC: At 278 nm with a purity of 96%.

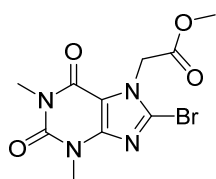
[000215] Compound 72: 2-(1,3-diethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl) phenyl)acetamide.



Step 3: Preparation of 2-(1,3-diethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl)acetamide.

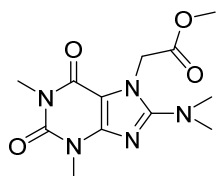
A stirred solution of 2-(2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl)acetamide (1 equiv.) in N,N-dimethylformamide (0.03 M) was added K_2CO_3 (2.5 equiv.) and stirred at room temperature for 15 min. Ethyl iodide (2.5 equiv.) was added to the reaction mixture and stirred for another 4 h at room temperature. After completion, water was added to the reaction mixture and extracted with ethyl acetate twice. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 , and concentrated under vacuum and purified by column chromatography to afford the product 2-(1,3-diethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl)acetamide as an off-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.48 (s, 1H), 8.08 (s, 1H), 7.70-7.68 (d, J = 8.4 Hz, 2H), 7.62-7.61 (m, 3H), 7.54-7.53 (d, J = 4.4 Hz, 1H), 5.21 (s, 2H), 4.06-4.04 (m, 2H), 3.89-3.87 (m, 2H), 1.27-1.23 (t, J = 6.8 Hz, 3H), 1.11-1.08 (t, J = 6.8 Hz, 3H). LC-MS: m/z 424.12 (M+H) with a purity of 99%.

[000216] Compound 73: 2-(8-(dimethylamino)-1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl)acetamide.



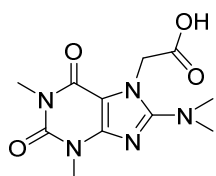
Step 1: Preparation of 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(3'-methoxybiphenyl-4-yl)acetamide.

Intermediate was prepared using alkylation method A reaction conditions as described. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 5.19 (s, 2H), 3.74 (s, 3H), 3.41 (s, 3H), 3.20 (s, 3H). LC-MS: m/z 332 (M+H).



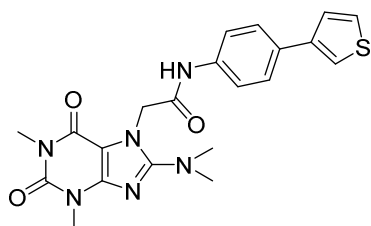
Step 2: Preparation of methyl 2-(8-(dimethylamino)-1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetate.

A solution of 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(3'-methoxybiphenyl-4-yl)acetamide (1 equiv.) in 11% dimethylamine in 2M ethanol solution (1 equiv.) was refluxed for 18 h. After consumption of starting material, the reaction mixture was concentrated in vacuo and extracted with dichloromethane twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude compound was purified by column chromatography to obtain the intermediate methyl 2-(8-(dimethylamino)-1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetate. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 5.00 - 4.98 (m, 2H), 3.71 (s, 3H), 3.38 (s, 3H), 3.16 (s, 3H), 2.93 (s, 6H). LC-MS: m/z 297 (M+H+41).



Step 3: Preparation of 2-(8-(dimethylamino)-1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetic acid.

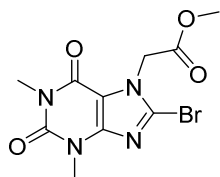
Intermediate was prepared using hydrolysis reaction conditions as described. LC-MS: m/z 282 (M+H).



Step 4: Preparation of 2-(8-(dimethylamino)-1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl)acetamide.

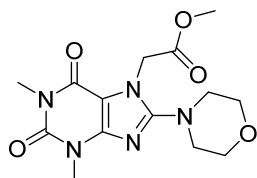
Product prepared using amide coupling method A reaction conditions as described. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.42 (s, 1H), 7.79-7.78 (m, 1H), 7.69 (s, 1H), 7.67 (s, 1H), 7.62-7.60 (m, 3H), 7.52 (dd, $J=5$ Hz, $J=1$ Hz, 1H), 5.02 (s, 2H), 3.41 (s, 3H), 3.17 (s, 3H), 2.97 (s, 6H). LC-MS: m/z 439 (M+H) with a purity of 97%.

[000217] Compound 74: 2-(1,3-dimethyl-8-morpholino-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl)acetamide.



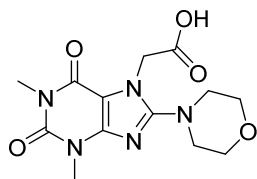
Step 1: Preparation of methyl 2-(8-bromo-1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetate.

Intermediate was prepared using alkylation method A reaction conditions as described. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 5.19 (s, 2H), 3.74 (s, 3H), 3.41 (s, 3H), 3.20 (s, 3H). LC-MS: m/z 332 (M+H).



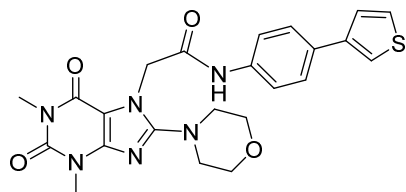
Step 2: Preparation of methyl 2-(1,3-dimethyl-8-morpholino-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetate.

A stirred solution of methyl 2-(8-bromo-1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetate (1 equiv.) and morpholine (5 equiv.) in DMF (0.4 M) was refluxed for 2 h. After consumption of starting material, the reaction mixture was quenched with water and extracted with dichloromethane twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude compound was purified by column chromatography to afford the intermediate methyl 2-(1,3-dimethyl-8-morpholino-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetate. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 4.94 (s, 2H), 3.71 - 3.69 (m, 6H), 3.17 (s, 3H), 3.39 (s, 3H), 3.16 - 3.13 (m, 5H). LC-MS: m/z 338 (M+H).



Step 3: Preparation of 2-(1,3-dimethyl-8-morpholino-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetic acid.

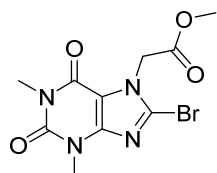
Intermediate was prepared using hydrolysis reaction conditions as described. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 4.83 (s, 2H), 3.72 - 3.70 (m, 3 H), 3.39 (s, 3H), 3.18 (s, 3H), 3.16 - 3.14 (m, 5H). LC-MS: m/z 324 (M+H).



Step 4: Preparation of 2-(1,3-dimethyl-8-morpholino-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl)acetamide.

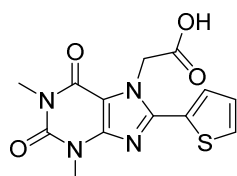
Product was prepared using amide coupling method A reaction conditions as described. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.45 (s, 1H), 7.79 (m, 1H), 7.69 - 7.67 (m, 2H), 7.63 - 7.60 (m, 3H), 7.52 (m, 1H), 4.97 (s, 2H), 3.70 (t, $J=4.4$ Hz, 4H), 3.42 (s, 3H), 3.21 (t, $J=4.4$ Hz, 4H), 3.19 (s, 3H). LC-MS: m/z 481 (M+H) with a purity of 99%.

[000218] Compound 75: 2-(1,3-dimethyl-2,6-dioxo-8-(thiophen-2-yl)-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl)acetamide.



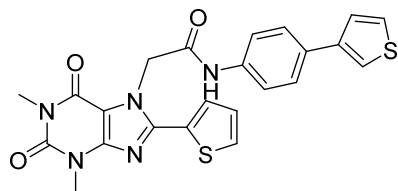
Step 1: Preparation of methyl 2-(8-bromo-1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetate.

Intermediate prepared using alkylation method A reaction conditions as described. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 5.19 (s, 2H), 3.74 (s, 3H), 3.41 (s, 3H), 3.20 (s, 3H). LC-MS: m/z 332 (M+H).



Step 2: Preparation of 2-(1,3-dimethyl-2,6-dioxo-8-(thiophen-2-yl)-2,3-dihydro-1H-purin-7(6H)-yl)acetic acid.

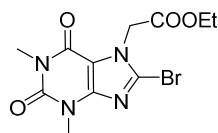
Intermediate prepared using Suzuki coupling method C reaction conditions as described. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.87 - 7.85 (m, 1H), 7.55 - 7.54 (m, 1H), 7.27 - 7.24 (m, 1H), 5.28 (s, 2H), 3.47 (s, 3H), 3.24 (s, 3H). LC-MS: m/z 321 (M+H).



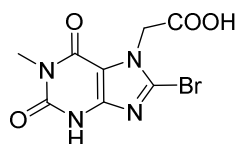
Step 3: Preparation of 2-(1,3-dimethyl-2,6-dioxo-8-(thiophen-2-yl)-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl)acetamide.

Product prepared using amide coupling method A reaction conditions as described. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.61 (s, 1H), 7.85 (dd, $J=5.0$ Hz, $J=1.2$ Hz, 1H), 7.80 - 7.79 (m, 1H), 7.70 - 7.68 (m, 2H), 7.62 - 7.59 (m, 4H), 7.54 (dd, $J=15.8$ Hz, $J=1.2$ Hz, 1H), 7.25 - 7.23 (m, 1H), 5.44 (s, 2H), 3.49 (s, 3H), 3.24 (s, 3H). LC-MS: m/z 478 (M+H) with a purity of 98%.

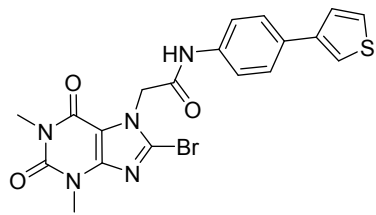
[000219] Compound 76: 2-(8-bromo-1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl)acetamide.



Step 1: Methyl 2-(8-bromo-1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetate. Intermediate prepared using alkylation method A reaction conditions as described. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 5.19 (s, 2H), 3.74 (s, 3H), 3.41 (s, 3H), 3.20 (s, 3H). LC-MS: m/z 332 (M+H).



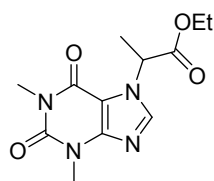
Step 2: 2-(8-bromo-1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetic acid. Intermediate was prepared using hydrolysis reaction conditions as described. ^1H NMR (400 MHz, DMSO-d_6): 13.60 (brs, 1H), 5.06 (s, 2H), 3.32 (s, 3H), 3.20 (s, 3H). LC-MS: m/z 316.94, 318.94 M-H, M-H+2) with a purity of 99%.



Step 3: 2-(8-bromo-1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl)acetamide.

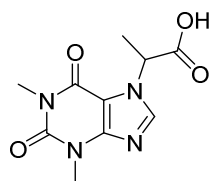
Product was prepared using amide coupling method A reaction conditions as described. ^1H NMR (400 MHz, DMSO-d_6): 10.57 (s, 1H), 7.80 (s, 1H), 7.70-7.68 (m, 2H), 7.62-7.59 (m, 3H), 7.52 (s, 1H), 5.20 (s, 2H), 3.43 (s, 3H), 3.21 (s, 3H). LC-MS: m/z 474.20 ($\text{M}+\text{H}$) with a purity of 96.04 %. HPLC: At 279 nm with a purity of 97%.

[000220] Compound 77: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(6-phenyl pyridazin-3-yl)propanamide.



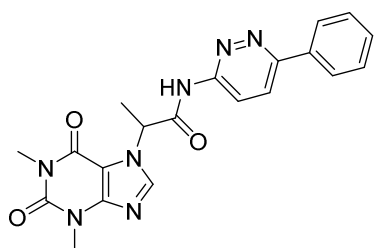
Step 1: Preparation of ethyl 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanoate.

Intermediate was prepared using Mitsunobu reaction conditions as described. LC-MS: m/z 281 ($\text{M}+\text{H}$) with a purity of 46%.



Step 2: Preparation of 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanoic acid.

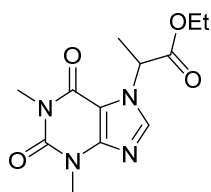
Intermediate was prepared using hydrolysis reaction conditions as described. ^1H -NMR (400 MHz; DMSO-d_6) δ (ppm): 13.27 (br s, 1H), 8.21 (s, 1H), 5.49-5.44 (q, $J = 7.5$ Hz, 1H), 3.44 (s, 3H), 3.21 (s, 3H), 1.76-1.74 (d, $J = 7.5$ Hz, 3H).



Step 3: Preparation of 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(6-phenylpyridazin-3-yl)propanamide.

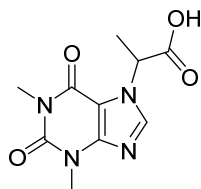
Product was prepared using amide coupling method A reaction conditions as described. ^1H -NMR (400 MHz; CDCl_3) δ (ppm): 11.78 (s, 1H), 8.50-8.46 (m, 1H), 8.02-8.00 (dd, $J = 6.8, 3.2$ Hz, 2H), 7.90-7.86 (m, 1H), 7.51-7.48 (m, 3H), 6.02-5.94 (q, $J = 7.6$ Hz, 1H), 3.61 (s, 3H), 3.44 (s, 3H), 1.97-1.95 (d, $J = 7.2$ Hz, 3H). MS (ESI): m/z 406.21 $[\text{M} + \text{H}]^+$.

[000221] Compound 78: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(6-(4-fluoro phenyl)pyridazin-3-yl)propanamide.



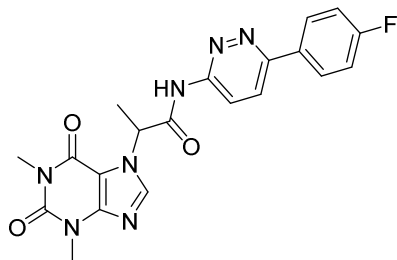
Step 1: Preparation of ethyl 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanoate.

Intermediate was prepared using Mitsunobu reaction conditions as described. LC-MS: m/z 281 (M+H) with a purity of 46%.



Step 2: Preparation of 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanoic acid.

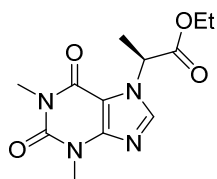
Intermediate was prepared using hydrolysis reaction conditions as described. ^1H -NMR (400 MHz; $\text{DMSO}-d_6$) δ (ppm): 13.27 (br s, 1H), 8.21 (s, 1H), 5.49-5.44 (q, $J = 7.5$ Hz, 1H), 3.44 (s, 3H), 3.21 (s, 3H), 1.76-1.74 (d, $J = 7.5$ Hz, 3H).



Step 3: Preparation of 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(6-(4-fluorophenyl)pyridazin-3-yl)propanamide.

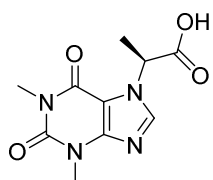
Product was prepared using amide coupling method A reaction conditions as described. ^1H -NMR (400 MHz; CDCl_3) δ (ppm): 10.39 (s, 1H), 8.46-8.44 (d, $J = 9.2$ Hz, 1H), 8.03-8.00 (m, 2H), 7.88 (s, 1H), 7.84-7.82 (d, $J = 9.2$ Hz, 1H), 7.21-7.16 (t, $J = 8.4$ Hz, 2H), 5.91-5.87 (q, $J = 7.1$ Hz, 1H), 3.60 (s, 3H), 3.45 (s, 3H), 1.96-1.94 (d, $J = 7.1$ Hz, 3H). MS (ESI): m/z 422 $[\text{M}+\text{H}]^+$.

[000222] Compound 79: (S)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl)propanamide.



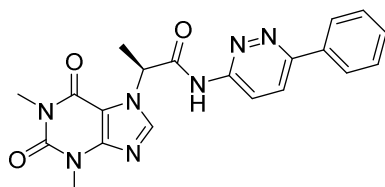
Step 1: Preparation of (S)-ethyl 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanoate.

Intermediate was prepared using Mitsunobu reaction conditions as described. ^1H -NMR (400 MHz; $\text{DMSO}-d_6$) δ (ppm): 7.76 (s, 1H), 5.62 (q, $J = 7.6$ Hz, 1H), 4.25 (q, $J = 6.8$ Hz, 2H), 3.61 (s, 3H), 3.39 (s, 3H), 1.85 (d, $J = 7.6$ Hz, 3H), 1.29 (d, $J = 7.2$ Hz, 3H). MS (ESI): m/z 281 $[\text{M}+\text{H}]^+$. LC-MS: m/z 281 ($\text{M}+\text{H}$) with a purity of 48%.



Step 2: Preparation of (S)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanoic acid.

Intermediate was prepared using hydrolysis reaction conditions as described. ^1H -NMR (400 MHz; $\text{DMSO}-d_6$) δ (ppm): 13.28 (brs, 1H), 8.21 (s, 1H), 5.47 (q, $J = 7.6$ Hz, 1H), 3.44 (s, 3H), 3.21 (s, 3H), 1.75 (d, $J = 7.6$ Hz, 3H). MS (ESI): m/z 253.3 $[\text{M}+\text{H}]^+$. LC-MS: Purity of 99 %

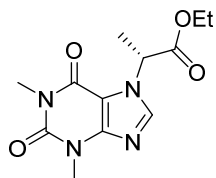


Step 3: Preparation of (S)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(6-phenylpyridazin-3-yl)propanamide.

Product was prepared using amide coupling method A reaction conditions as described. ^1H -NMR (400 MHz; $\text{DMSO}-d_6$) δ (ppm): 11.78 (s, 1H), 8.35 (s, 1H), 8.27 (dd, $J = 9.2$ Hz, $J = 9.2$

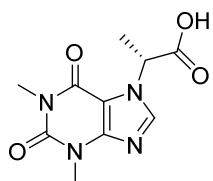
Hz, 2H), 8.1 (d, $J = 6.4$ Hz, 2H), 7.57-7.51 (m, 3H), 5.84 (d, $J = 7.6$ Hz, 1H), 3.46 (s, 3H), 3.19 (s, 3H), 1.9 (d, $J = 7.6$ Hz, 3H). MS (ESI): m/z 406.21 $[M+H]^+$. LC-MS: Purity of 97%.

[000223] Compound 80: (R)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiophen-3-yl)phenyl)propanamide.



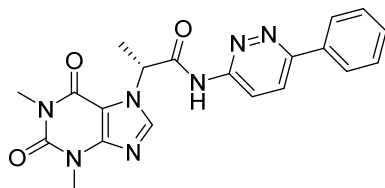
Step 1: Preparation of (R)-ethyl 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanoate.

Intermediate was prepared using Mitsunobu reaction conditions as described. $^1\text{H-NMR}$ (400 MHz; DMSO- d_6) δ (ppm): 7.76 (s, 1H), 5.62 (q, $J = 7.6$ Hz, 1H), 4.25 (q, $J = 6.8$ Hz, 2H), 3.61 (s, 3H), 3.39 (s, 3H), 1.85 (d, $J = 7.6$ Hz, 3H), 1.29 (d, $J = 7.2$ Hz, 3H). MS (ESI): m/z 281 $[M+H]^+$. LC-MS: m/z 281 (M+H) with a purity of 48%.



Step 2: Preparation of (R)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanoic acid.

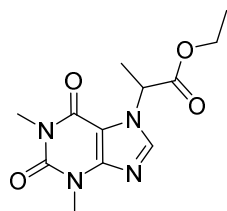
Intermediate prepared using hydrolysis reaction conditions as described. $^1\text{H-NMR}$ (400 MHz; DMSO- d_6) δ (ppm): 13.28 (brs, 1H), 8.21 (s, 1H), 5.47 (q, $J = 7.6$ Hz, 1H), 3.44 (s, 3H), 3.21 (s, 3H), 1.75 (d, $J = 7.6$ Hz, 3H). MS (ESI): m/z 253.3 $[M+H]^+$. LC-MS: Purity of 99%



Step 3: Preparation of (R)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(6-phenylpyridazin-3-yl)propanamide.

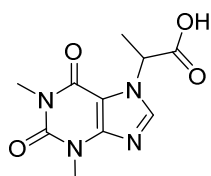
Product was prepared using amide coupling method A reaction conditions as described. $^1\text{H-NMR}$ (400 MHz; CDCl_3) δ (ppm): 10.61 (s, 1H), 8.47 (d, $J = 9.6$ Hz, 1H), 8.01 (dd, $J = 2.4$ Hz, $J = 5.6$ Hz, 2H), 7.89 (s, 1H), 7.86 (s, 1H), 7.49 (d, $J = 6.8$ Hz, 3H), 5.98 (d, $J = 6.8$ Hz, 1H), 3.61 (s, 3H), 3.43 (s, 3H), 1.96 (d, $J = 7.6$ Hz, 3H). MS (ESI): m/z 406.21 $[M+H]^+$. LC-MS: Purity of 97%.

[000224] Compound 81: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiazol-2-yl) phenyl)propanamide.



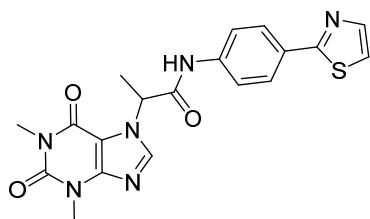
Step 1: Preparation of ethyl 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanoate.

Intermediate was prepared using alkylation method A reaction conditions as described. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.20 (s, 1H), 5.55 (q, $J=7.2$ Hz, 1H), 4.14 (q, $J=7.2$ Hz, 2H), 3.45 (s, 3H), 3.21 (s, 3H), 1.75 (d, $J=7.2$ Hz, 3H), 1.17 (t, $J=7.2$ Hz, 3H). LC-MS: m/z 281 (M+H)



Step 2: Preparation of 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanoic acid.

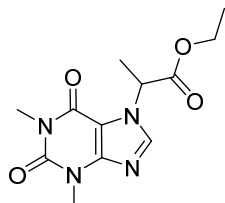
Intermediate was prepared using hydrolysis reaction conditions as described. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.20 (s, 1H), 5.47 (q, $J=7.2$ Hz, 1H), 3.44 (s, 3H), 3.21 (s, 3H), 1.75 (d, $J=7.2$ Hz, 3H). LC-MS: m/z 253 (M+H)



Step 3: Preparation of 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(thiazol-2-yl)phenyl)propanamide.

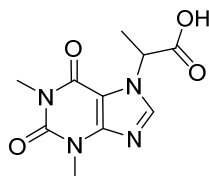
Product was prepared using amide coupling method D reaction conditions as described. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.65 (s, 1H), 8.33 (s, 1H), 7.93 - 7.91 (m, 2H), 7.88 (d, $J=3.2$ Hz, 1H), 7.73 - 7.72 (m, 2H), 7.70 (m, 1H), 5.73 - 5.68 (q, $J=7.2$ Hz, 1H), 3.46 (s, 3H), 3.20 (s, 3H), 1.85 (d, $J=7.2$ Hz, 3H). LC-MS: m/z 411 (M+H) with a purity of 99%.

[000225] Compound 82: 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(6-(thiazol-2-yl) pyridin-3-yl)propanamide.



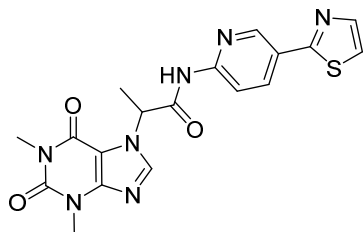
Step 1: Preparation of ethyl 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanoate.

Intermediate was prepared using alkylation method A reaction conditions as described. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.97 (s, 1H), 5.59 (q, $J = 7.60$ Hz, 1H), 4.24 (q, $J = 7.20$ Hz, 2H), 3.58 (s, 3H), 3.36 (s, 3H), 1.83 (d, $J = 7.60$ Hz, 3H), 1.28 (t, $J = 7.20$ Hz, 3H). LC-MS: m/z 281 (M+H).



Step 2: Preparation of 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)propanoic acid.

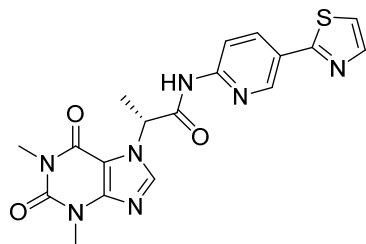
Intermediate was prepared using hydrolysis reaction conditions as described. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 8.19 (s, 1H), 5.46 (q, $J = 7.20$ Hz, 1H), 3.44 (s, 3H), 3.21 (s, 3H), 1.74 (d, $J = 7.20$ Hz, 3H). LC-MS: m/z 253 (M+H).



Step 3: Preparation of 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(6-(thiazol-2-yl)pyridin-3-yl)propanamide.

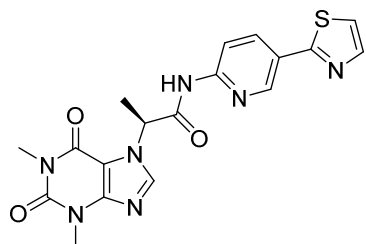
Product was prepared using amide coupling method E reaction conditions as described. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 11.30 (s, 1H), 8.93 (s, 1H), 8.30 – 8.32 (m, 2H), 8.09 – 8.11 (m, 1H), 7.95 (d, $J = 2.00$ Hz, 1H), 7.82 (d, $J = 2.00$ Hz, 1H), 5.80 (q, $J = 7.20$ Hz, 3H), 3.46 (s, 3H), 3.19 (s, 3H), 1.86 (d, $J = 7.20$ Hz, 3H). LC-MS: m/z 412 (M+H) with a purity of 97%.

[000226] Compound 83: (R)-2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)-N-(5-(thiazol-2-yl)pyridin-2-yl)propanamide.



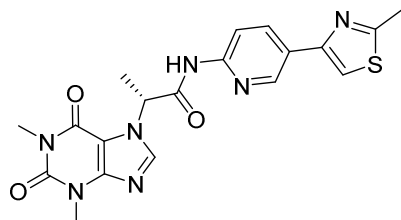
Product was prepared using chiral separation of the racemate. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 11.30 (s, 1H), 8.93 (s, 1H), 8.30 – 8.32 (m, 2H), 8.09 - 8.11 (m, 1H), 7.95 (d, J = 2.00 Hz, 1H), 7.82 (d, J = 2.00 Hz, 1H), 5.80 (q, J = 7.20 Hz, 3H), 3.46 (s, 3H), 3.19 (s, 3H), 1.86 (d, J = 7.20 Hz, 3H).

[000227] Compound 84: (S)-2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)-N-(5-(thiazol-2-yl)pyridin-2-yl)propanamide.



[000228] Product was prepared using chiral separation of the racemate. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 11.30 (s, 1H), 8.93 (s, 1H), 8.30 – 8.32 (m, 2H), 8.09 - 8.11 (m, 1H), 7.95 (d, J = 2.00 Hz, 1H), 7.82 (d, J = 2.00 Hz, 1H), 5.80 (q, J = 7.20 Hz, 3H), 3.46 (s, 3H), 3.19 (s, 3H), 1.86 (d, J = 7.20 Hz, 3H).

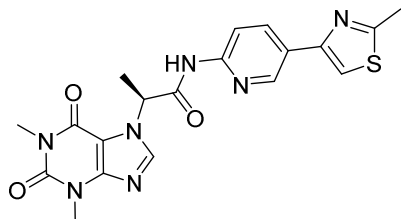
[000229] Compound 85: (R)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(5-(2-methylthiazol-4-yl)pyridin-2-yl)propanamide



Product was prepared using amide coupling method A reaction conditions as described. The isomers were separated by chiral preparative HPLC to give (R)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(5-(2-methylthiazol-4-yl)pyridin-2-yl)propanamide, ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 11.18 (1H, s), 8.94-8.93 (1H, d, J = 2.4Hz), 8.33 (1H, s), 8.30-

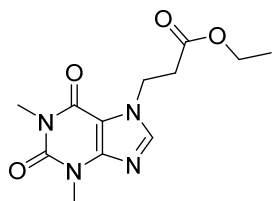
8.27 (1H, dd, $J_1=2.4$ Hz, $J_2 = 6.4$ Hz), 8.05-8.03 (1H, d, $J = 8.8$ Hz), 8.01 (1H, s), 5.80-5.78 (1H, m) 3.45 (3H, s), 3.19 (3H, s), 2.72 (3H, s), 1.86-1.84 (3H, d, $J = 7.6$ Hz). LC-MS: m/z 426.12 (M+H) with a purity of 97.84 %. HPLC: At 254 nm with a purity of 97%. Chiral HPLC: 99%. Specific Rotation: + 137 deg

[000230] Compound 86: (S)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(5-(2-methylthiazol-4-yl)pyridin-2-yl)propanamide.



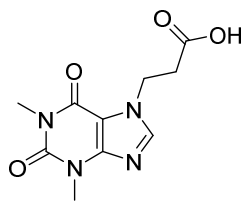
Product was prepared using amide coupling method A reaction conditions as described. The isomers were separated by chiral preparative HPLC to give 100 mg of (S)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(5-(2-methylthiazol-4-yl)pyridin-2-yl)propanamide. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 11.18 (s, 1H), 8.94-8.93 (d, $J = 2.4$ Hz, 1H), 8.33 (s, 1H), 8.30-8.27 (dd, $J_1=2.4$ Hz, $J_2 = 6.4$ Hz, 1H), 8.05-8.03 (d, $J = 8.8$ Hz, 1H), 8.01 (s, 1H), 5.80-5.78 (q, $J = 7.5$ Hz, 1H) 3.45 (s, 3H), 3.19 (s, 3H), 2.72 (s, 3H), 1.86-1.84 (d, $J = 7.6$ Hz, 3H). LC-MS: m/z 426.12 (M+H) with a purity of 98.38 %. HPLC: At 254 nm with a purity of 97%. Chiral HPLC: 99%. Specific Rotation: -127 deg

[000231] Compound 87: 3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)-N-(4-(thiophen-3-yl)phenyl)propanamide.



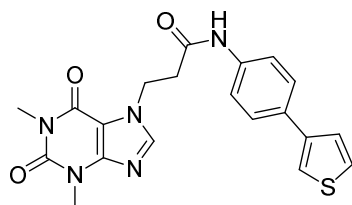
Step 1: Preparation of ethyl 3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)propanoate.

The intermediate was prepared using alkylation conditions. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): 8.03 (s, 1H), 4.46 (t, $J=6.8$ Hz, 2H), 4.05 (q, $t=6.6$ Hz, 2H), 3.42 (s, 3H), 3.24 (s, 3H), 2.93 (t, $J=6.6$ Hz, 2H), 1.15 (t, $J=6.8$ Hz, 3H). LC-MS: m/z 281 (M+H).



Step 2: Preparation of 3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)propanoic acid.

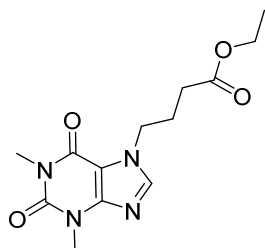
^1H NMR (400 MHz, DMSO- d_6): 8.01 (s, 1H), 4.43 (t, $J=6.8$ Hz, 2H), 3.42 (s, 3H), 3.24 (s, 3H), 2.84 (t, $J=6.8$ Hz, 2H). LC-MS: m/z 253 ($M+H$)



Step 3: Preparation of 3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)-N-(4-(thiophen-3-yl)phenyl)propanamide.

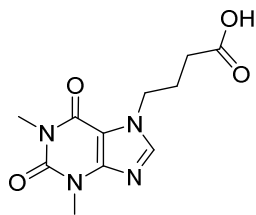
^1H NMR (400 MHz, DMSO- d_6): 9.99 (s, 1H), 8.00 (s, 1H), 7.75 (br s, 1H), 7.64 - 7.55 (m, 5H), 7.51 - 7.49 (d, $J=5.2$ Hz, 1H), 4.54 (t, $J=6.4$ Hz, 2H), 3.42 (s, 3H), 2.96 (t, $J=6.4$ Hz, 2H). LC-MS: m/z 410 ($M+H$) with a purity of 99%.

[000232] Compound 88: 4-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)-N-(4-(thiophen-3-yl)phenyl)butanamide.



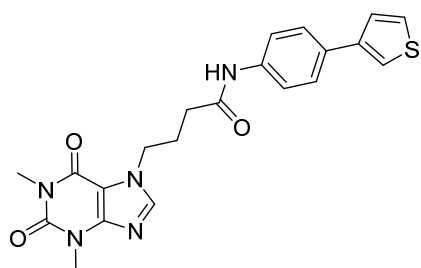
Step 1: Preparation of ethyl 4-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)butanoate.

The intermediate was prepared using alkylation conditions. ^1H NMR (400 MHz, CDCl_3 - d) δ 7.55 (s, 1H), 4.37 (t, $J = 6.80$ Hz, 2H), 4.13 (q, $J = 7.20$ Hz, 2H), 3.59 (s, 3H), 3.41 (s, 3H), 2.32 (t, $J = 6.80$ Hz, 2H), 2.21 (p, $J = 6.80$ Hz, 2H), 1.25 (q, $J = 7.20$ Hz, 3H). LC-MS: m/z 295 ($M+H$) with a purity of 98%.



Step 2: Preparation of 4-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)butanoic acid.

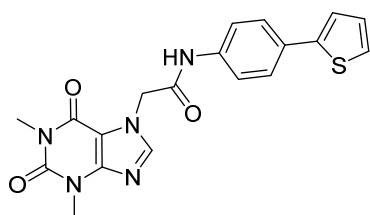
The intermediate was prepared using hydrolysis conditions. ^1H NMR (400 MHz, DMSO- d_6) δ 8.05 (s, 1H), 4.26 (t, J = 7.20 Hz, 2H), 3.42 (s, 3H), 3.22 (s, 3H), 2.19 (t, J = 7.20 Hz, 2H), 2.01 (q, J = 7.20 Hz, 2H). LC-MS: m/z 267 ($\text{M}+\text{H}$).



Step 3: Preparation of 4-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)-N-(4-(thiophen-3-yl)phenyl)butanamide.

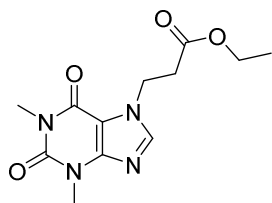
The final product is prepared using amide coupling method A reaction conditions. ^1H NMR (Methanol- d_4) δ 7.92 (s, 1H), 7.53 – 7.57 (m, 3H), 7.47 – 7.50 (m, 2H), 7.43 – 7.45 (m, 1H), 7.40 – 7.41 (m, 1H), 4.45 (t, J = 6.80 Hz, 2H), 3.45 (s, 3H), 3.33 (s, 3H), 2.43 (t, J = 6.80 Hz, 2H), 2.31 (p, J = 6.80 Hz, 2H). LCMS (ESI) m/z 424 (MH^+) with a purity of 97%.

[000233] Compound 89: 2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)-N-(4-(thiophen-2-yl)phenyl)acetamide.



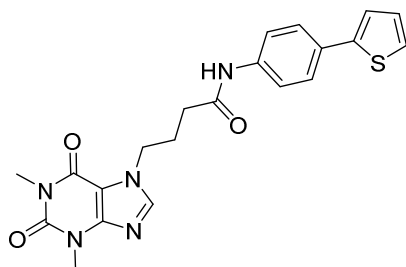
^1H NMR (400 MHz, DMSO- d_6): 10.48 (s, 1H), 8.07 (s, 1H), 7.62 (s, 4H), 7.49 (d, J =5.2 Hz, 1H), 7.43 (d, J =3.6 Hz, 1H), 7.11 (m, 1H), 5.22 (s, 2H), 3.47 (s, 3H), 3.21 (s, 3H). LC-MS: m/z 396 ($\text{M}+\text{H}$) with a purity of 97%.

[000234] Compound 90: 3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)-N-(4-(thiophen-2-yl)phenyl)propanamide.



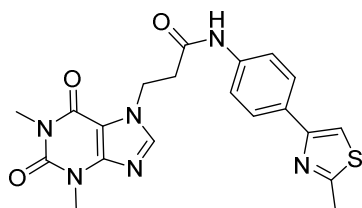
^1H NMR (400 MHz, DMSO-d_6): 10.05 (s, 1H), 8.00 (s, 1H), 7.57 (s, 4H), 7.47 (d, $J=5.2$ Hz, 1H), 7.40 (d, $J=3.6$ Hz, 1H), 7.10 (t, $J=4.2$ Hz, 1H), 4.54 (t, $J=6.4$ Hz, 2H), 3.42 (s, 3H), 3.26 (s, 3H), 2.96 (t, $J=6.4$ Hz, 2H). LC-MS: m/z 410 ($\text{M}+\text{H}$) with a purity of 97%.

[000235] Compound 91: 4-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)-N-(4-(thiophen-2-yl)phenyl)butanamide.



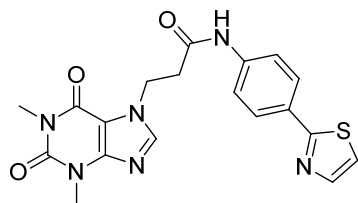
^1H NMR (Methanol- d_4) δ 7.92 (s, 1H), 7.47 – 7.55 (m, 4H), 7.30 – 7.32 (m, 2H), 7.06 (t, $J = 4.40$ Hz, 1H), 4.45 (t, $J = 6.80$ Hz, 2H), 3.45 (s, 3H), 3.33 (s, 3H), 2.43 (t, $J = 6.80$ Hz, 2H), 2.30 (p, $J = 6.80$ Hz, 2H). LCMS (ESI) m/z 424 (MH^+). LCMS (ESI) m/z 424 (MH^+) with a purity of 98%.

[000236] Compound 92: 3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)-N-(4-(2-methylthiazol-4-yl)phenyl)propanamide.



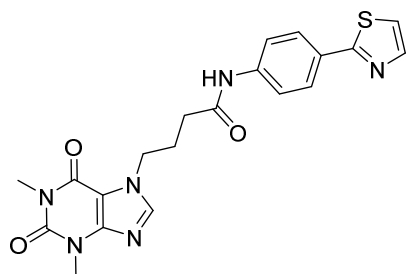
^1H NMR (400 MHz, Methanol- d_4) δ 7.92 (s, 1H), 7.78 – 7.80 (m, 2H), 7.54 – 7.55 (m, 3H), 4.67 (t, $J = 6.00$ Hz, 2H), 4.55 (bs, 1H), 3.52 (s, 3H), 3.37 (s, 3H), 3.01 (t, $J = 6.00$ Hz, 2H), 2.73 (s, 3H). LC-MS: m/z 425 ($\text{M}+\text{H}$) with a purity of 99%.

[000237] Compound 93: 3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)-N-(4-(thiazol-2-yl)phenyl)propanamide.



^1H NMR (400 MHz, DMSO- d_6) δ 10.17 (s, 1H), 8.00 (s, 1H), 7.85 – 7.88 (m, 3H), 7.65 – 7.70 (m, 3H), 4.54 (t, J = 6.40 Hz, 2H), 3.42 (s, 3H), 2.99 (t, J = 6.40 Hz, 2H). LC-MS: m/z 411 (M+H) with a purity of 99%.

[000238] Compound 94: 4-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)-N-(4-(thiazol-2-yl)phenyl)butanamide.



^1H NMR (400 MHz, Methanol- d_4) δ 7.95 (s, 1H), 7.86 (d, J = 8.80 Hz, 2H), 7.82 (d, J = 3.20 Hz, 1H), 7.61 (d, J = 8.80 Hz, 2H), 7.55 (d, J = 3.20 Hz, 1H), 4.45 (t, J = 6.80 Hz, 2H), 3.45 (s, 3H), 3.33 (s, 3H), 2.45 (t, J = 6.80 Hz, 2H), 2.31 (p, J = 6.80 Hz, 2H). LC-MS: m/z 425 (M+H) with a purity of 96%.

Application example 1

Materials and Methods:

Cell lines and culture conditions:

[000239] HEK293-STF cell line was modified from Human embryonic kidney cell line HEK293 transfected with the STF reporter. HEK293-STF3A cell line was further modified from HEK293-STF cell line to express Wnt3A. This cell line was used to identify compounds that regulate either early or late signalling components of the Wnt pathway. L-Wnt3A (ATCC, #CRL-2647) cell line was used for providing Wnt3A conditioned media. The three cell lines were grown in DMEM (Dulbecco's Modified Eagle Medium) with 10% FBS (fetal bovine serum) incubated in 37°C with 5% CO_2 .

Cell viability assay:

[000240] 5000 cells in 75 µl culture media were seeded in each well of black 96 well plates (Greiner #655090) and incubated overnight at 37°C. 25 µl of serially diluted compound was added to the cells giving final concentration of 50 µM to 1.5 nM. After 1 day of treatment, 100 µl of CellTiter-Glo® Luminescent Cell Viability Assay reagent (#G7571, Promega) was added to each well and incubated for 10 minutes at room temperature. Luminescence was measured using Tecan Safire2® microplate reader.

STF3A assay:

[000241] 2×10^4 HEK293-STF3A cells in 75 µl culture media were seeded in each well of white 96 well plates (Greiner #655098) and incubated overnight at 37°C. 25 µl serially diluted compound was added to the cells to give final concentration of 50 µM to 1.5 nM. After 1 day of treatment, 100 µl of Steady-Glo® Luciferase Assay reagent (#E2520, Promega) was added to each well and incubated for 10 minutes at room temperature. Luminescence was measured using Tecan Safire2® plate reader.

STF/WNT3A conditioned medium (STF/WNT3A CM) assay:

[000242] L-Wnt3A cells were cultured in three T-175 flasks at 3×10^4 cells/ml in 30 ml culture medium per flask. After 4 days of incubation, the Wnt3A conditioned media were harvested and then centrifuged at 2000 rpm for 10 minutes to remove the debris. The Wnt3A conditioned media were stored at -20°C if not used immediately.

[000243] 2×10^4 HEK293-STF cells in 25 µl culture media were added in each well of white 96 well plates (Greiner #655098). 25 µl serially diluted compound was added to the cells. After 4 hours of incubation, 100 µl Wnt-3A conditioned medium was added to the cells. The final concentration of compound ranged from 33 µM to 1 nM. After incubation for 1 day at 37°C, 100 µl of Steady-Glo® Luciferase Assay reagent (#E2520, Promega) was added to each well and incubated for 10 minutes at room temperature. Luminescence was measured using Tecan Safire2® microplate reader.

Results:

Compound	STF3A IC50 μ M
1	<0.1
2	<0.1
3	<1
4	<1
5	<0.1
6	<1
7	>10
8	<5
9	<0.1
10	<1
11	<0.1
12	<5
13	>10
14	<1
15	<0.1
16	<1
17	>10
18	<0.1
19	<0.1
20	<0.1
21	<0.1
22	<0.1
23	<0.1
24	<1
25	<0.1
26	<0.1
27	>10
28	>10
29	<0.1
30	<0.1
31	<5
32	<0.1
33	<0.1
34	<0.1
35	<0.1
36	<0.1
37	<0.1
38	<0.1
39	>10
40	<1
41	<0.1
42	>10
43	>10
44	>10
45	<0.1
46	<1
47	<1

Compound	STF3A IC50 μ M
48	<1
49	<1
50	<1
51	<1
52	<1
53	<0.1
54	<0.1
55	<5
56	<1
57	<0.1
58	>10
59	<0.1
60	<1
61	<0.1
62	<0.1
63	<1
64	<0.1
65	>10
66	<0.1
67	<1
68	<0.1
69	<0.1
70	<0.1
71	>10
72	<0.1
73	<0.1
74	<1
75	<1
76	<0.1
77	<0.1
78	<1
79	<0.1
80	>10
81	<0.1
82	<0.1
83	<10
84	<0.1
85	<5
86	<0.1
87	<0.1
88	<0.1
89	<0.1
90	<0.1
91	<0.1
92	<1
93	<1
94	<1

MMTV-WNT1 Tumor Model:

[000244] To test the *in vivo* efficacy of Compound 5 to prevent the growth of Wnt driven tumors, fragments from two independent MMTV-WNT1 tumors were orthotopically transplanted into female nude mice. The mice were treated with either vehicle or Compound 5, 30 mg/kg once daily for 19 days. Tumor volumes were measured on alternate days. Treatment with Compound 5 decreased tumor growth in all the treated mice. A significant decrease in tumor weights collected at sacrifice was also observed. Results are shown in Fig. 1.

Cytoplasmic and nuclear β -catenin Experiment

[000245] Result: Compound 5 decreased cytoplasmic and nuclear β -catenin in tumors. Staining the tumor sections for β -catenin showed that vehicle treated tumors had abundant β -catenin in cytoplasm and nucleus. Two representative samples from each treatment arm are shown in Fig. 2.

Phospho-LRP6 assay as a target efficacy marker for Compound 5

[000246] Palmitoylation of Wnts is essential for Wnt/ β -Catenin signaling. Once Wnts are palmitoylated by the O-acyl transferase porcupine they are secreted and subsequently bind to the receptor complex, consisting of Frizzled (cognate receptors) and the co-receptor LRP5 or LRP6 (Cadigan and Peifer, 2009). LRP5 and LRP6 are highly homologous single-pass transmembrane proteins of the low-density lipoprotein receptor (LDLR)-related protein family. Upon Wnt binding LRP is phosphorylated on multiple sites (including Thr 1479, Ser 1490 and Thr1493) by kinases such as Casein Kinase 1 (CK1), Glycogen Synthase Kinase 3 (GSK3) or MEK1 (Cervenka et al., 2011; Tamai et al., 2004; Zeng et al., 2005). Phosphorylated LRP then recruits axin to the membrane and subsequently activates β -Catenin signalling.

[000247] The present target efficacy biomarker assay measures a decrease in levels of p-LRP6 (i.e. phosphorylated LRP-6) (Ser1490) upon treatment with a porcupine inhibitor (Compound 5). Cells treated with 2 μ M of the test compound *in vitro* showed a greater than 50% reduction in p-LRP6 from 4 h onwards, with no decrease observed in total LRP levels (Fig. 3). The inhibitory effect remains up to 72 h (data not shown) in the presence of the compound and up to 12 h after the compound has been removed (data not shown).

[000248] While 2 μ M led to 50-60% inhibition after 6 h of *in vitro* treatment, 3.3 nM of Compound 5 still inhibited p-LRP6 (Ser1490) by about 20% in this assay (Fig. 4). Concentrations lower than 3.3 nM did not inhibit p-LRP6 in HPAF-II pancreatic adenocarcinoma cells (data not shown).

[000249] The inventors have validated that this assay works alike for cancer cells and tumour tissue (data not shown).

[000250] References:

Cadigan, K.M., and Peifer, M. (2009). Wnt signaling from development to disease: insights from model systems. *Cold Spring Harbor perspectives in biology* 1, a002881.

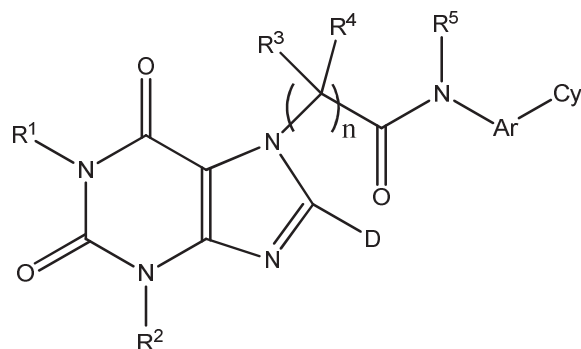
Cervenka, I., Wolf, J., Masek, J., Krejci, P., Wilcox, W.R., Kozubik, A., Schulte, G., Gutkind, J.S., and Bryja, V. (2011). Mitogen-activated protein kinases promote WNT/beta-catenin signaling via phosphorylation of LRP6. *Molecular and cellular biology* 31, 179-189.

Tamai, K., Zeng, X., Liu, C., Zhang, X., Harada, Y., Chang, Z., and He, X. (2004). A mechanism for Wnt coreceptor activation. *Molecular cell* 13, 149-156.

Zeng, X., Tamai, K., Doble, B., Li, S., Huang, H., Habas, R., Okamura, H., Woodgett, J., and He, X. (2005). A dual-kinase mechanism for Wnt co-receptor phosphorylation and activation. *Nature* 438, 873-877.

CLAIMS

1. A compound having structure (I)



(I)

wherein:

R^1 , R^2 , R^3 , R^4 and R^5 are each, independently, H or an alkyl group;

D is selected from the group consisting of H, halogen, alkyl, cycloalkyl, aryl, and dialkylamino, each, other than H and halogen, being optionally substituted;

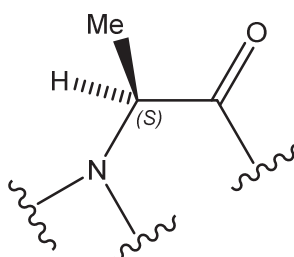
Ar is a 6-membered heteroaryl ring having 1 or 2 nitrogen atoms having no substituents other than Cy and the amide nitrogen atom, these being in a 1,4-relationship on said ring; and

Cy is an aryl, heteroaryl or a saturated ring containing at least one heteroatom, each being optionally substituted; and

n is an integer from 1 to 2,

or an enantiomer, diastereomer or salt thereof.

2. The compound of claim 1, wherein, if $n=1$ and one of R^3 and R^4 is methyl and the other is H, the stereochemistry of the compound is as shown in partial structure (II):

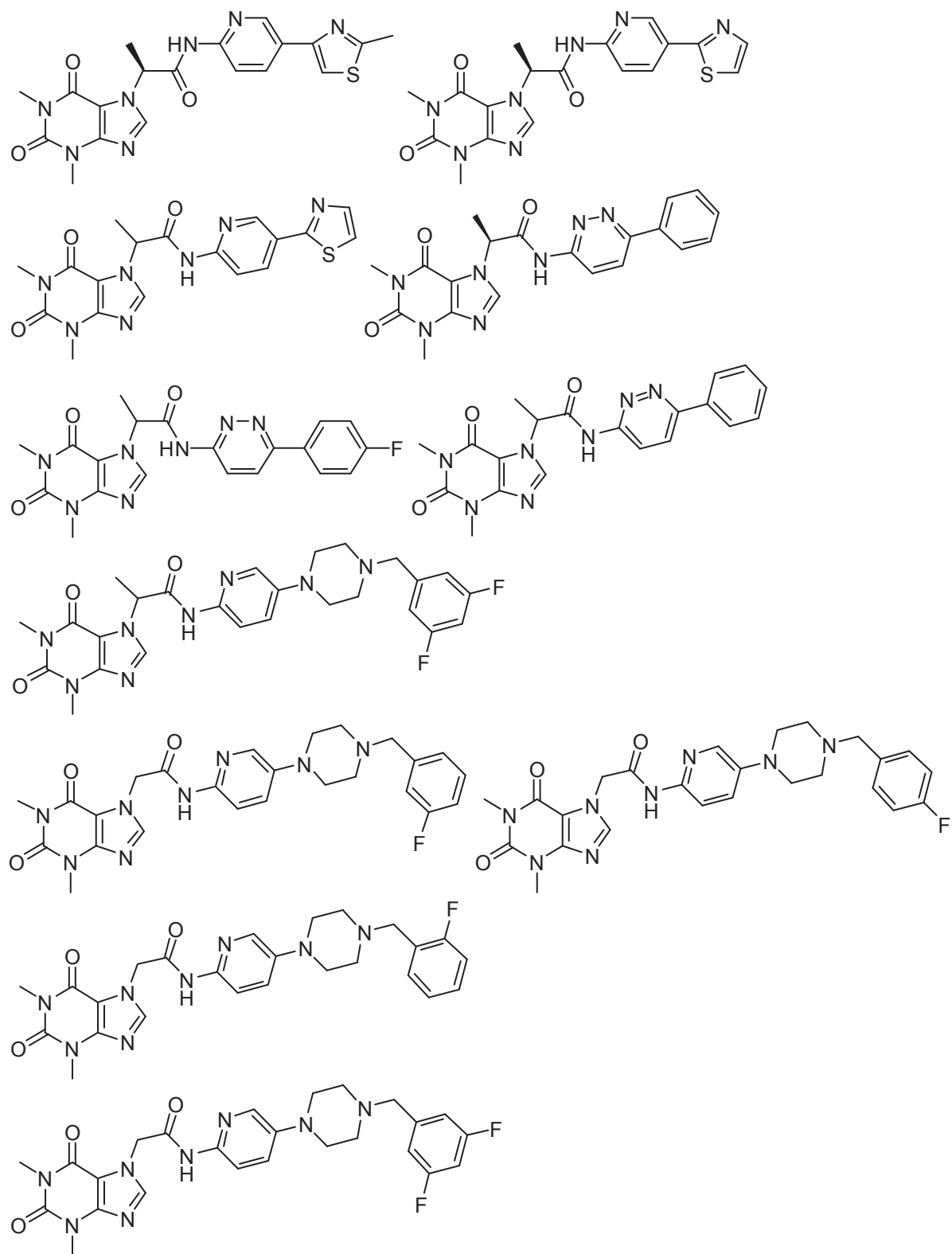


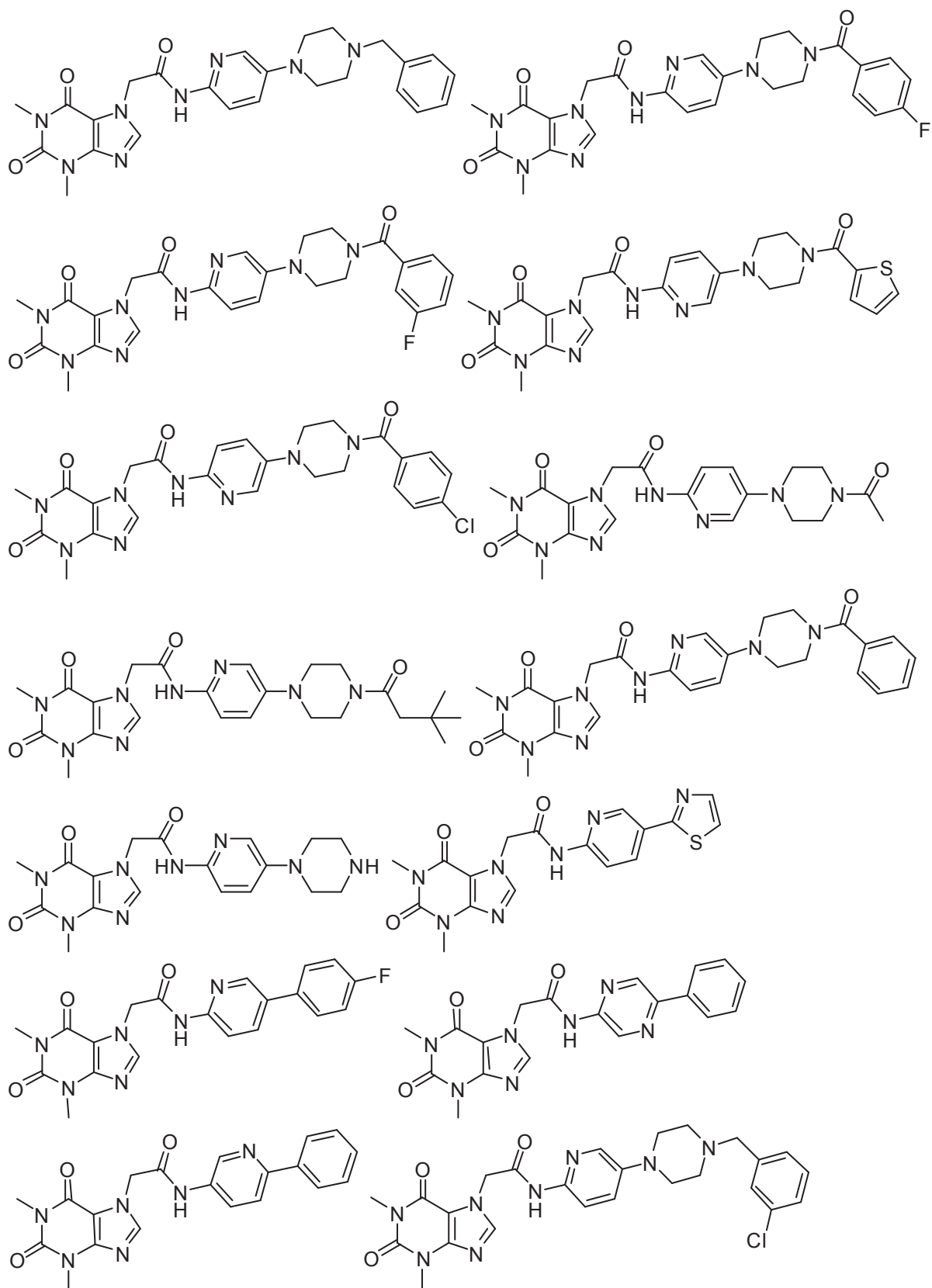
(II).

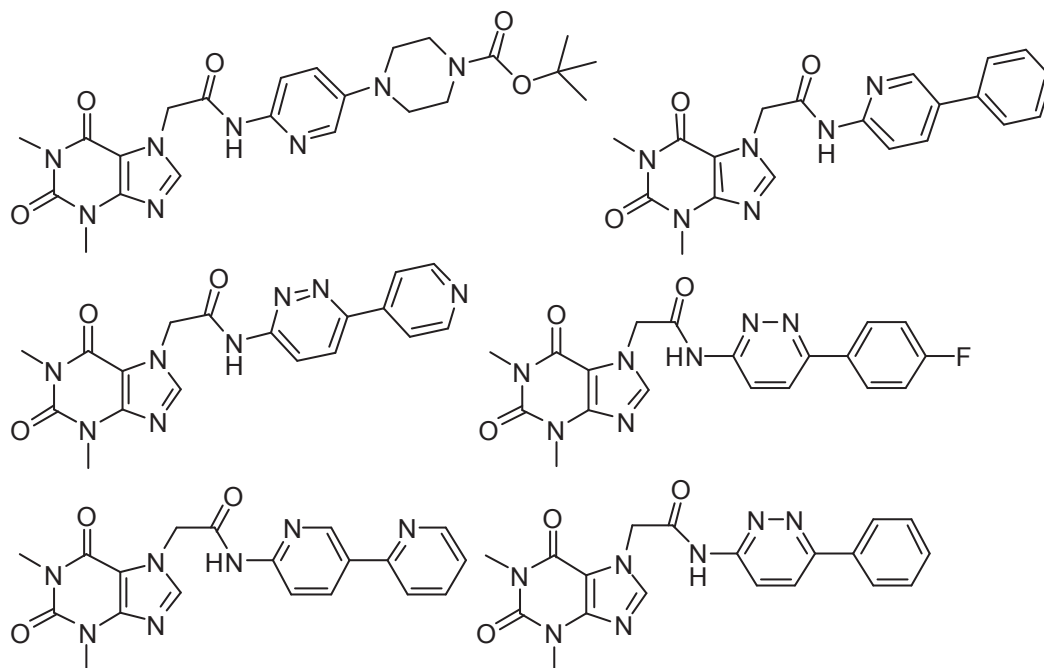
3. The compound of claim 1 wherein R^1 and R^2 are the same.
4. The compound of any one of claims 1 to 3 wherein R^1 and R^2 are both methyl.
5. The compound of any one of claims 1 to 3 wherein R^1 and R^2 are both ethyl.
6. The compound of any one of claims 1 to 5 wherein Cy is a 5 or 6 membered aromatic ring having between 0 and 2 nitrogen atoms, 0 or 1 sulfur atoms and 0 or 1 oxygen atoms.
7. The compound of any one of claims 1 to 6 wherein Cy is piperazine, substituted on both nitrogen atoms.
8. The compound of any one of claims 1 to 7 wherein n is 1.
9. The compound of any one of claims 1 to 8 wherein D is H.
10. The compound of any one of claims 1 to 9 wherein R^1 and R^2 are both methyl, R^3 , R^4 , R^5 and D are all H and n is 1.
11. The compound of any one of claims 1 to 8 in which D is methyl, cyclopropyl, trifluoromethyl, phenyl, dimethylamino, morpholin-N-yl, thiophene-3-yl or bromo.
12. The compound of any one of claims 1 to 11 wherein R^3 and R^4 are either both H or both methyl.
13. The compound of any one of claims 1 to 11 wherein one of R^3 and R^4 is H and the other is methyl or ethyl.
14. The compound of any one of claims 1 to 13 wherein R^5 is H.
15. The compound of claim 1 in which R^1 and R^2 are both Me, D is H, n is 1 and R^3 and R^4 are both H.
16. The compound of any one of claims 1 to 15 having IC_{50} against STF3A of less than 10 micromolar, optionally less than 5 micromolar.

17. The compound of any one of claims 1 to 16 which does not inhibit TRPA1 at an IC_{50} of 10 micromolar, optionally 5 micromolar.

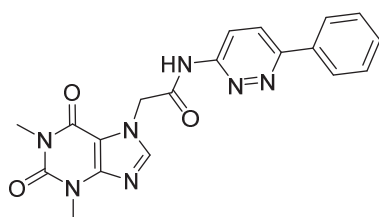
18. The compound of claim 1 which is one of the following:







19. The compound of claim 1 which is:



20. The compound of any one of claims 1 to 19 for use in the treatment of a disease or condition associated with Wnt pathway activity.

21. The compound of claim 20 wherein the disease or condition is selected from a cancer, such as cervical, colon, breast, bladder, head and neck, gastric, lung, ovarian, prostate, thyroid, non-small-cell lung, chronic lymphocytic leukemia, mesothelioma, melanoma, pancreatic adenocarcinoma, basal cell carcinoma, osteosarcoma, hepatocellular carcinoma, Wilm's tumor or medulloblastoma; a fibrotic disease, such as pulmonary fibrosis, liver fibrosis, skin fibrosis or renal fibrosis; a degenerative disease; or a metabolic disease such as diabetic retinopathy.

22. Use of a compound according to any one of claims 1 to 19 in the manufacture of a medicament for the treatment of a disease or condition associated with Wnt pathway activity, said disease or condition being selected from the group consisting of cancer, such as

cervical, colon, breast, bladder, head and neck, gastric, lung, ovarian, prostate, thyroid, non-small-cell lung, chronic lymphocytic leukemia, mesothelioma, melanoma, pancreatic adenocarcinoma, basal cell carcinoma, osteosarcoma, hepatocellular carcinoma, Wilm's tumor or medulloblastoma; a fibrotic disease, such as pulmonary fibrosis, liver fibrosis, skin fibrosis or renal fibrosis; a degenerative disease; or a metabolic disease such as diabetic retinopathy.

23. The use of claim 22 wherein the disease or condition is selected from the group consisting of cancer, fibrosis, stem cell and diabetic retinopathy, rheumatoid arthritis, psoriasis and myocardial infarction.

24. The use of claim 22 or claim 23 wherein the cancer is characterised by high Wnt activity or a fibrotic disease or a degenerative disease.

25. A pharmaceutical composition comprising a compound according to any one of claims 1 to 19 together with one or more pharmaceutically acceptable carriers, diluents or adjuvants.

26. An anhydrous form of the free base of 2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)-N-(6-phenylpyridazin-3-yl)acetamide.

27. The anhydrous form of claim 26 which is a non-hydrated single polymorph.

28. The anhydrous form of claim 26 or claim 27 which is crystalline.

29. The anhydrous form of claim 28 which shows on X-ray diffraction a peak on the 2theta scale at $22.2^{\circ} \pm 0.5^{\circ}$.

30. The anhydrous form of claim 28 or claim 29 which shows on X-ray diffraction peaks on the 2theta scale at $5.5^{\circ} \pm 0.5^{\circ}$ and $14.2^{\circ} \pm 0.5^{\circ}$.

31. The anhydrous form of any one of claims 28 to 30 which shows on X-ray diffraction at least four peaks on the 2theta scale selected from the group consisting of $5.5^{\circ} \pm 0.5^{\circ}$ and $12.5^{\circ} \pm 0.5^{\circ}$, $14.2^{\circ} \pm 0.5^{\circ}$, $16.7^{\circ} \pm 0.5^{\circ}$, $17.7^{\circ} \pm 0.5^{\circ}$, $18.8^{\circ} \pm 0.5^{\circ}$, $22.4^{\circ} \pm 0.5^{\circ}$, $24.2^{\circ} \pm 0.5^{\circ}$ and $31.7^{\circ} \pm 0.5^{\circ}$.

32. The anhydrous form of any one of claims 28 to 31 which shows on X-ray diffraction peaks on the 2theta scale of and $5.5^{\circ} \pm 0.5^{\circ}$ and $12.5^{\circ} \pm 0.5^{\circ}$, $14.2^{\circ} \pm 0.5^{\circ}$, $16.7^{\circ} \pm 0.5^{\circ}$, $17.7^{\circ} \pm 0.5^{\circ}$, $18.0^{\circ} \pm 0.5^{\circ}$, $18.8^{\circ} \pm 0.5^{\circ}$, $19.6^{\circ} \pm 0.5^{\circ}$, $20.6^{\circ} \pm 0.5^{\circ}$, $22.4^{\circ} \pm 0.5^{\circ}$, $24.2^{\circ} \pm 0.5^{\circ}$, $24.4^{\circ} \pm 0.5^{\circ}$, $25.0^{\circ} \pm 0.5^{\circ}$, $27.0^{\circ} \pm 0.5^{\circ}$, $27.6^{\circ} \pm 0.5^{\circ}$, $29.8^{\circ} \pm 0.5^{\circ}$, $31.7^{\circ} \pm 0.5^{\circ}$ and $32.2^{\circ} \pm 0.5^{\circ}$.
33. A pharmaceutical composition comprising an anhydrous free base according to any one of claims 26 to 32.
34. Use of an anhydrous free base according to any one of claims 26 to 32 in the manufacture of a medicament for the treatment of a proliferative disorder associated with Wnt pathway activity, said disorder selected from cancer, such as cervical, colon, breast, bladder, head and neck, gastric, lung, ovarian, prostate, thyroid, non-small-cell lung, chronic lymphocytic leukemia, mesothelioma, melanoma, pancreatic adenocarcinoma, basal cell carcinoma, osteosarcoma, hepatocellular carcinoma, Wilm's tumor or medulloblastoma; a fibrotic disease, such as pulmonary fibrosis, liver fibrosis, skin fibrosis or renal fibrosis; a degenerative disease; or a metabolic disease such as diabetic retinopathy.
35. Use according to claim 34 wherein the proliferative disorder is cancer.