Novel Heterocyclic Derivatives

Field of the Invention

The invention relates to purine derivatives and pharmaceutically acceptable salts thereof, processes for their preparation, their use in the treatment of diseases, their use, either alone or in combination with at least one additional therapeutic agent and optionally in combination with a pharmaceutically acceptable carrier, for the manufacture of pharmaceutical preparations, use of the pharmaceutical preparations for the treatment of diseases, and a method of treatment of said diseases, comprising administering the purine derivatives to a warm-blooded animal, especially a human.

Background of the Invention

The phosphatidylinositol-3-kinases superfamily comprises 4 different PI3K related lipid or protein kinases. Class I, II and III are lipid kinases that differ by virtue of their substrate specificities whereas class IV PI3Ks (also called PIKKs) are protein kinases. Class I phosphatidylinositol-3-kinases comprise a family of lipid kinases that catalyze the transfer of phosphate to the D-3' position of inositol lipids to produce phosphoinositol-3-phosphate (PIP), phosphoinositol-3,4-diphosphate (PIP_2) and phosphoinositol-3,4,5-triphosphate (PIP_3) that, in turn, act as second messengers in signaling cascades by docking proteins containing pleckstrin-homology, FYVE, Phox and other phospholipid-binding domains into a variety of signaling complexes often at the plasma membrane ((Vanhaesebroeck et al., *Annu. Rev. Biochem* 70:535 (2001); Katso et al., *Annu. Rev. Cell Dev. Biol.* 17:615 (2001)). Of the two Class I PI3Ks, Class IA PI3Ks are heterodimers composed of a catalytic p110 subunit (α β, δ, isoforms) constitutively associated with a regulatory subunit that can be p85α, p55α, p50α, p85β or p55γ. The Class IB sub-class has one family member, a heterodimer composed of a catalytic p110γ subunit associated with one of two regulatory subunits, p101 or p84 (Fruman et al., *Annu Rev. Biochem.* 67:481 (1998); Suire et al., *Curr. Biol.* 15:566 (2005)). The modular domains of the p85/55/50 subunits include Src Homology (SH2) domains that bind phosphotyrosine residues in a specific sequence context on activated receptor and cytoplasmic tyrosine kinases, resulting in activation and localization of Class IA PI3Ks. Class IB PI3K is activated directly by G protein-coupled receptors that bind a diverse repertoire of peptide and non-peptide ligands (Stephens et al., *Cell* 89:105 (1997)); Katso et al., *Annu. Rev. Cell Dev. Biol.* 17:615-675 (2001)). Consequently, the resultant phospholipid products of class I PI3K link upstream receptors with downstream cellular activities including proliferation, survival, chemotaxis, cellular trafficking, motility, metabolism, inflammatory and allergic responses, transcription and translation (Cantley et al., *Cell* 64:281 (1991); Escobedo and Williams, *Nature* 335:85 (1988); Fantl et al., *Cell* 69:413 (1992)).

In many cases, PIP2 and PIP3 recruit Akt, the product of the human homologue of the viral oncogene *v-Akt*, to the plasma membrane where it acts as a nodal point for many intracellular signaling pathways important for growth and survival (Fantl et al., *Cell* 69:413-423(1992); Bader et al., *Nature Rev. Cancer* 5:921 (2005); Vivanco and Sawyer, *Nature Rev. Cancer* 2:489 (2002)). Aberrant regulation of PI3K, which often increases survival through Akt activation, is one of the most prevalent events in human cancer and has been shown to occur at multiple levels. The tumor suppressor gene *PTEN*, which dephosphorylates phosphoinositides at the 3' position of the inositol ring and in so doing antagonizes PI3K activity, is functionally deleted in a variety of tumors. In other tumors, the genes for the p110α isoform, *PIK3CA*, and for *Akt* are amplified and increased protein expression of their gene products has been demonstrated in several human cancers. Furthermore, mutations and translocation of p85α that serve to up-regulate the p85-p110 complex have been described in human cancers. Also, somatic missense mutations in *PIK3CA* that activate downstream signaling pathways have been described at significant frequencies in a wide diversity of human cancers (Kang at al., *Proc. Natl. Acad. Sci. USA* 102:802 (2005); Samuels et al., *Science* 304:554 (2004); Samuels et al., *Cancer Cell* 7:561-573 (2005)). These observations show that deregulation of phosphoinositol-3 kinase and the upstream and downstream components of this signaling pathway is one of the most common deregulations associated with human cancers and proliferative diseases (Parsons et al., *Nature* 436:792 (2005); Hennessey at el., *Nature Rev. Drug Disc.* 4:988-1004 (2005)).

The mammalian target of rapamycin (mTOR) is a member of the class IV PI3K. mTOR assembles a signaling network that transduces nutrient signals and various other stimuli to regulate a wide range of cellular functions including cell growth, proliferation, survival, autophagy, various types of differentiation and metabolism. In mammalian cells, the mTOR protein is found complexed in two distinct entities called mTORC1 and mTORC2. The mTORC1 complex, that is to say mTOR associated with raptor, has been the matter of numerous studies. It is mTORC1 that integrates nutrient and growth factor inputs, and is in turn responsible for cell growth regulation, mainly through protein synthesis regulators such as 4EBP1 or RPS6. mTORC1 regulation requires PI3K and Akt activation for activation, meaning that mTORC1 is an effector of the PI3K pathway. mTOR when associated in the mTOR complex 2 (mTORC2) has been shown to be responsible for the activation of Akt by phosphorylation of S473 (Akt 1 numbering) (Sarbassov et al., Science 307:7098 (2005)). mTORC2 is hence here considered as an upstream activator of Akt. Interestingly mTOR can therefore be considered as being important both upstream and downstream of Akt. mTOR

catalytic inhibiton might therefore represent a unique way of addressing a very strong block in the PI3K-Akt pathway, by addressing both upstream and downstream effectors.

A link between mTOR inhibition and autophagy has also been demonstrated (Ravikumar et al., *Nat Genet.* 36(6):585-95 (2004)). Autophagy is essential for neuronal homeostasis and its dysfunction has been linked to neurodegeneration. Loss of autophagy in neurons causes neurodegenerative disease in mice (Komatsu et al., *Nature* 441:880-4 (2006); Hara et al., *Nature 441:885-9 (2006)*) suggesting a critical role for autophagy to maintain protein homeostasis in neurons. Neurodegenerative diseases are characterized by inclusions of misfolded proteins as one of the hallmarks. Induction of autophagy enhances clearance of misfolded proteins and thus is proposed as therapy for neurodegenerative proteinopathies.

Huntington`s Disease (HD) is an autosomal dominant neurodegenerative disorder where a mutation of IT15 gene encoding the Huntingtin (Htt) protein leads to Polyglutamine expansion in Exon1 of Htt. Intracellular aggregation of this mutant Htt protein and brain atrophy (in particular cortex and striatum) are the main hallmarks of HD. It clinically leads to movement disturbance and cognitive dysfunction besides psychiatric disturbances and weight loss.

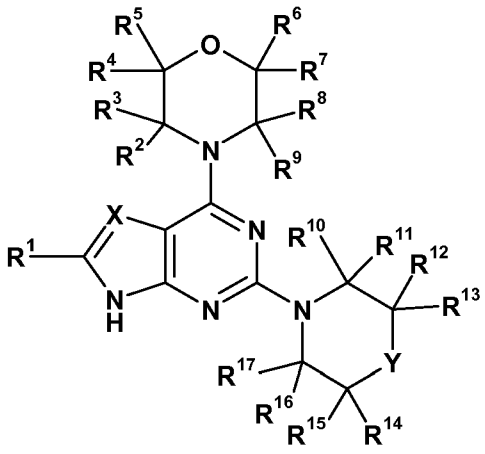
Inhibition of mTOR induces autophagy and reduces mutant Htt aggregation and mutant Htt-mediated cell death in *in vitro* and *in vivo* models of HD (Ravikumar et al., *Nat Genet.* 36(6):585-95 (2004)). mTOR inhibition therefore provides an opportunity for pharmaceutical intervention and modulation of the disrupted cellular processes characteristic of HD.

In view of the above, inhibitors of class I PI3Ks and mTOR are considered to be of value in the treatment of proliferative diseases and other disorders, in particular, HD.

The present invention relates to novel purine derivatives having class I PI3K and/or mTOR inhibitory activity, their preparation, medical use and to medicaments comprising them.

Summary of the Invention

In a first aspect, the invention relates to a compound of formula (I), or a pharmaceutically acceptable salt thereof,

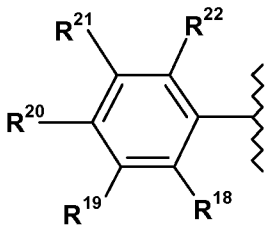


(I)

wherein

X represents N or CH;

R^1 represents



wherein

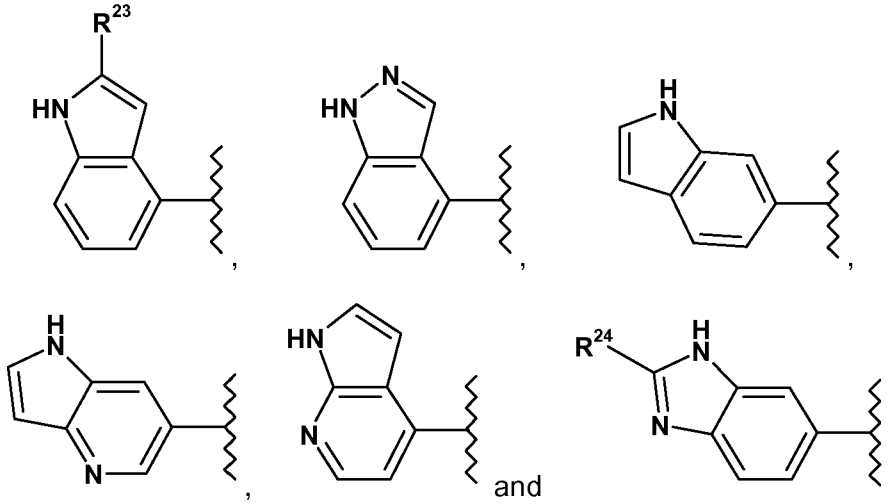
R^{18} and R^{22} independently represent hydrogen, halogen, hydroxy or hydroxy-C_{1-3}alkyl-;

R^{19} and R^{21} independently represent hydrogen, amino, hydroxy, carboxy, C_{1-3}alkoxy, amino-C_{1-3}alkyl-, C_{1-3}alkyl-C(=O)-NH-, C_{1-3}alkyl-$S(=O)_m$-NH- or hydroxy-C_{1-3}alkyl-;

m represents 0, 1 or 2;

R^{20} represents hydrogen, halogen or C_{1-3}alkoxy; or

R^1 is selected from the group consisting of



wherein

R^{23} represents hydrogen or methyl;

R^{24} represents hydrogen, oxo or C_{1-3}alkyl;

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} independently represent hydrogen or methyl;

or R^2 and R^8 together form an ethylene bridge;

or R^2 and R^6 together form a methylene bridge;

or R^{12} and R^{14} together form an ethylene bridge; and

Y represents O, CHR^{25} or $CR^{26}R^{27}$

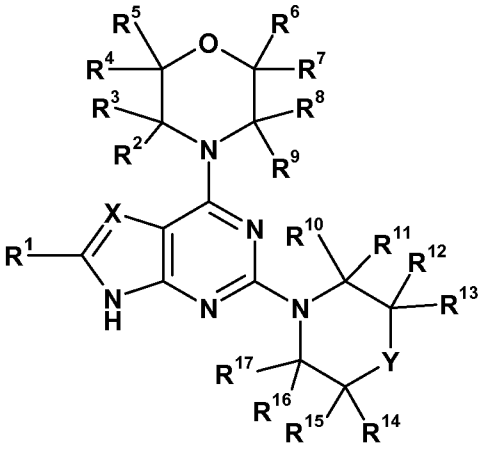
wherein

R^{25} represents hydroxy or C_{1-3}alkoxy; and

R^{26} and R^{27} independently represent hydrogen or halogen;

with the proviso that the compound of formula (I) is other than 2,6-di-morpholin-4-yl-8-phenyl-9H-purine.

In a second aspect, the invention relates to a compound of formula (I), or a pharmaceutically acceptable salt thereof,

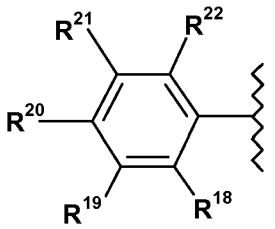


(I)

wherein

X represents N or CH;

R^1 represents



wherein

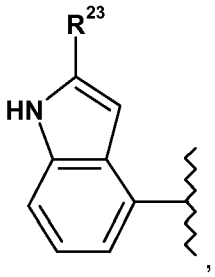
R^{18} and R^{22} independently represent hydrogen, halogen, hydroxy or hydroxy-C_{1-3}alkyl-;

R^{19} and R^{21} independently represent hydrogen, amino, hydroxy, carboxy, C_{1-3}alkoxy, amino-C_{1-3}alkyl-, C_{1-3}alkyl-C(=O)-NH-, C_{1-3}alkyl-$S(=O)_m$-NH- or hydroxy-C_{1-3}alkyl-;

m represents 0, 1 or 2;

R^{20} represents hydrogen, halogen or C_{1-3}alkoxy; or

R^1 is selected from the group consisting of



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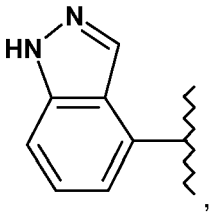

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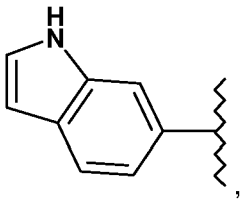

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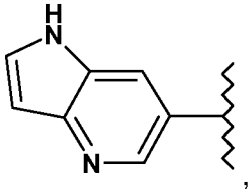

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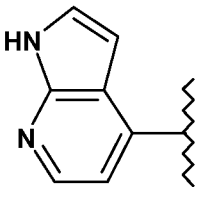
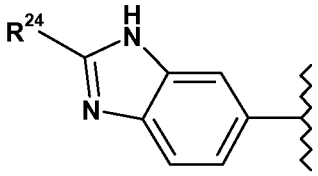


and


wherein

R^{23} represents hydrogen or methyl;

R^{24} represents hydrogen, oxo or C_{1-3}alkyl;

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} independently represent hydrogen or methyl; or R^5 and R^6 together form an ethylene bridge; and

Y represents O, CHR^{25} or $CR^{26}R^{27}$

wherein

R^{25} represents hydroxy or C_{1-3}alkoxy; and

R^{26} and R^{27} independently represent hydrogen or halogen;

with the proviso that the compound of formula (I) is other than 2,6-di-morpholin-4-yl-8-phenyl-9H-purine.

Definitions

As used herein, the term “halogen” or “halo” refers to fluoro, chloro, bromo, and iodo.

As used herein, the term “C_{1-3}alkyl” refers to a fully saturated branched or unbranched hydrocarbon moiety having up to 3 carbon atoms. Representative examples of C_{1-3}alkyl include methyl, ethyl, *n*-propyl and *iso*-propyl.

As used herein, the term “C_{1-3}alkoxy” refers to C_{1-3}alkyl-O-, wherein C_{1-3}alkyl is as defined herein above. Representative examples of C_{1-3}alkoxy include methoxy, ethoxy, propoxy and 2-propoxy.

As used herein, the term "hydroxy-C_{1-3}alkyl" refers to a C_{1-3}alkyl group as defined herein above, wherein one of the hydrogen atoms of the C_{1-3}alkyl group is replaced by OH. Representative examples of hydroxy-C_{1-3}alkyl include, but are not limited to, hydroxyl-methyl, 2-hydroxy-ethyl, 2-hydroxy-propyl and 3-hydroxy-propyl.

As used herein, the term "amino-C_{1-3}alkyl" refers to a C_{1-3}alkyl group as defined herein above, wherein one of the hydrogen atoms of the C_{1-3}alkyl group is replaced by a primary amino group. Representative examples of hydroxy-C_{1-3}alkyl include, but are not limited to, amino-methyl, 2-amino-ethyl, 2-amino-propyl and 3-amino-propyl.

Detailed Description of the Invention

The present invention provides compounds and pharmaceutical formulations thereof that may be useful in the treatment or prevention of diseases, conditions and/or disorders modulated by the inhibition of class I PI3Ks and/or mTOR.

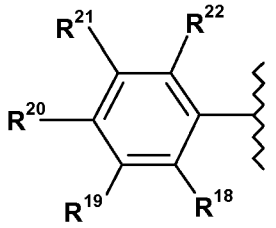
Embodiment 1: a compound of formula (I), or a pharmaceutically acceptable salt thereof, as described hereinbefore.

Embodiment 2: a compound of formula (I), or a pharmaceutically acceptable salt thereof, as described hereinbefore.

Embodiment 3: a compound according to Embodiment 1 or Embodiment 2, or a pharmaceutically acceptable salt thereof, wherein X represents N.

Embodiment 4: a compound according to Embodiment 1 or Embodiment 2, or a pharmaceutically acceptable salt thereof, wherein X represents CH.

Embodiment 5: a compound according to any one of Embodiments 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R^1 represents



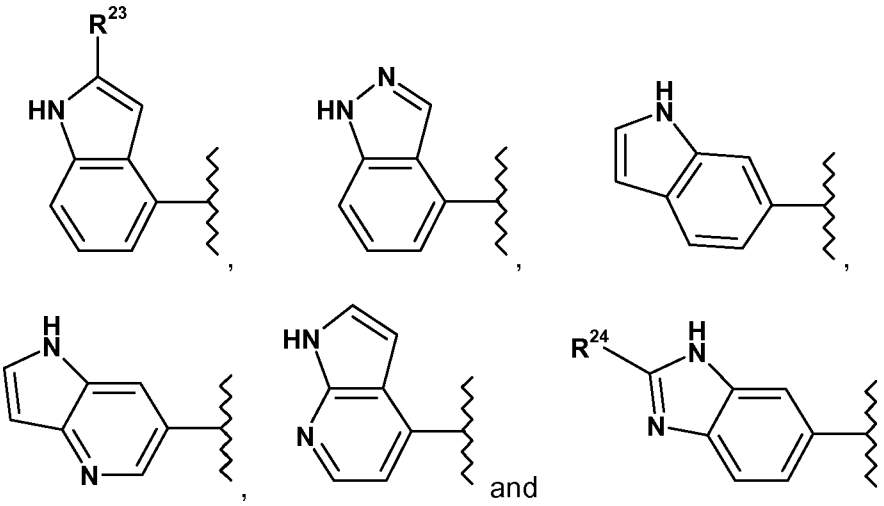
wherein

R^{18} and R^{22} independently represent hydrogen, halogen, hydroxy or hydroxy-C_{1-3}alkyl-;

R^{19} and R^{21} independently represent hydrogen, amino, hydroxy, carboxy, C_{1-3}alkoxy, amino-C_{1-3}alkyl-, C_{1-3}alkyl-C(=O)-NH-, C_{1-3}alkyl-$S(=O)_m$-NH- or hydroxy-C_{1-3}alkyl-;
m represents 0, 1 or 2; and
R^{20} represents hydrogen, halogen or C_{1-3}alkoxy.

Embodiment 6: a compound according to Embodiment 5, or a pharmaceutically acceptable salt thereof, wherein at least one of R^{18}, R^{19}, R^{20}, R^{21} and R^{22} is not hydrogen.

Embodiment 7: a compound according to any one of Embodiments 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from the group consisting of



and

wherein
R^{23} represents hydrogen or methyl; and
R^{24} represents hydrogen, oxo or C_{1-3}alkyl.

Embodiment 8: a compound according to any one of Embodiments 1 to 7, or a pharmaceutically acceptable salt thereof, wherein Y represents O;

Embodiment 9: a compound according to any one of Embodiments 1 to 7, or a pharmaceutically acceptable salt thereof, wherein Y represents CHR^{26} or $CR^{27}R^{28}$.

Embodiment 10: a compound according to Embodiment 1 or Embodiment 2, which is selected from:
3-[2-(2,6-Dimethyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purin-8-yl]-phenol;
3-(2,4-dimorpholino-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenol;
2,6-Bis-(3-methyl-morpholin-4-yl)-8-(1H-pyrrolo[2,3-b]pyridin-4-yl)-9H-purine;
{2-Fluoro-5-[6-(3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purin-8-yl]-phenyl}-methanol;
2-(4,4-Difluoro-piperidin-1-yl)-8-(1H-indol-4-yl)-6-(3-methyl-morpholin-4-yl)-9H-purine;

5-[2,6-Bis-(3-methyl-morpholin-4-yl)-9H-purin-8-yl]-1,3-dihydro-benzoimidazol-2-one;
{5-[2,6-Bis-(3-methyl-morpholin-4-yl)-9H-purin-8-yl]-2-methoxy-phenyl}-methanol;
8-(1H-Indol-4-yl)-2-morpholin-4-yl-6-(8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl)-9H-purine;
2-Methoxy-5-[6-(3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purin-8-yl]-benzoic acid;
{4-Chloro-3-[6-(3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purin-8-yl]-phenyl}-methanol;
3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-benzylamine;
1-{3-[6-(3-Methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purin-8-yl]-phenyl}-ethanol;
2,6-Di-morpholin-4-yl-8-(1H-pyrrolo[3,2-b]pyridin-6-yl)-9H-purine;
8-(1H-Indol-6-yl)-2,6-bis-(3-methyl-morpholin-4-yl)-9H-purine;
8-(1H-Indol-4-yl)-2,6-bis-(3-methyl-morpholin-4-yl)-9H-purine;
1-[8-(1H-Indol-4-yl)-6-(3-methyl-morpholin-4-yl)-9H-purin-2-yl]-piperidin-4-ol;
{3-[2,6-Bis-(3-methyl-morpholin-4-yl)-9H-purin-8-yl]-5-methoxy-phenyl}-methanol;
8-(1H-Indol-4-yl)-2-(3-methyl-morpholin-4-yl)-6-(3-methyl-morpholin-4-yl)-9H-purine;
{3-[2,6-Bis-(3-methyl-morpholin-4-yl)-9H-purin-8-yl]-4-fluoro-phenyl}-methanol;
8-(1H-Indol-4-yl)-6-(3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purine;
8-(1H-Indol-6-yl)-6-(3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purine;
8-(1H-Indol-4-yl)-2,6-bis-(3-methyl-morpholin-4-yl)-9H-purine;
8-(1H-Indol-4-yl)-6-(3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purine;
8-(1H-Indol-6-yl)-6-(3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purine;
8-(1H-Indol-4-yl)-2-(4-methoxy-piperidin-1-yl)-6-morpholin-4-yl-9H-purine;
8-(1H-Indol-4-yl)-2,6-di-morpholin-4-yl-9H-purine;
8-(1H-Indazol-4-yl)-2,6-di-morpholin-4-yl-9H-purine;
8-(1H-Indol-6-yl)-2,6-di-morpholin-4-yl-9H-purine;
3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenylamine;
N-[3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenyl]-acetamide;
8-(2-Methyl-1H-indol-4-yl)-2,6-di-morpholin-4-yl-9H-purine;
3-[2-(2,6-Dimethyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purin-8-yl]-phenylamine;
N-[3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenyl]-methanesulfonamide;
{2-[2-(2,6-Dimethyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purin-8-yl]-phenyl}-methanol;
[2-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenyl]-methanol;
3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenol;
[3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenyl]-methanol;
2-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenol;
3-[2-(2,6-Dimethyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purin-8-yl]-phenol;

3-(2,4-dimorpholino-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenol;

2,6-Bis-(3-methyl-morpholin-4-yl)-8-(1H-pyrrolo[2,3-b]pyridin-4-yl)-9H-purine;

{2-Fluoro-5-[6-(3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purin-8-yl]-phenyl}-methanol;

2-(4,4-Difluoro-piperidin-1-yl)-8-(1H-indol-4-yl)-6-(3-methyl-morpholin-4-yl)-9H-purine;

5-[2,6-Bis-(3-methyl-morpholin-4-yl)-9H-purin-8-yl]-1,3-dihydro-benzoimidazol-2-one;

{5-[2,6-Bis-(3-methyl-morpholin-4-yl)-9H-purin-8-yl]-2-methoxy-phenyl}-methanol;

8-(1H-Indol-4-yl)-2-morpholin-4-yl-6-(8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl)-9H-purine;

2-Methoxy-5-[6-(3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purin-8-yl]-benzoic acid;

{4-Chloro-3-[6-(3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purin-8-yl]-phenyl}-methanol;

3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-benzylamine;

1-{3-[6-(3-Methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purin-8-yl]-phenyl}-ethanol;

2,6-Di-morpholin-4-yl-8-(1H-pyrrolo[3,2-b]pyridin-6-yl)-9H-purine;

8-(1H-Indol-6-yl)-2,6-bis-(3-methyl-morpholin-4-yl)-9H-purine;

8-(1H-Indol-4-yl)-2,6-bis-(3-methyl-morpholin-4-yl)-9H-purine;

1-[8-(1H-Indol-4-yl)-6-(3-methyl-morpholin-4-yl)-9H-purin-2-yl]-piperidin-4-ol;

{3-[2,6-Bis-(3-methyl-morpholin-4-yl)-9H-purin-8-yl]-5-methoxy-phenyl}-methanol;

8-(1H-Indol-4-yl)-2-(3-methyl-morpholin-4-yl)-6-((S)-3-methyl-morpholin-4-yl)-9H-purine;

{3-[2,6-Bis-(3-methyl-morpholin-4-yl)-9H-purin-8-yl]-4-fluoro-phenyl}-methanol;

8-(1H-Indol-4-yl)-6-(3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purine;

8-(1H-Indol-6-yl)-6-(3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purine;

8-(1H-Indol-4-yl)-2,6-bis-(3-methyl-morpholin-4-yl)-9H-purine;

8-(1H-Indol-4-yl)-6-(3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purine;

8-(1H-Indol-6-yl)-6-(3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purine;

8-(1H-Indol-4-yl)-2-(4-methoxy-piperidin-1-yl)-6-morpholin-4-yl-9H-purine;

8-(1H-Indol-4-yl)-2,6-di-morpholin-4-yl-9H-purine;

8-(1H-Indazol-4-yl)-2,6-di-morpholin-4-yl-9H-purine;

8-(1H-Indol-6-yl)-2,6-di-morpholin-4-yl-9H-purine;

3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenylamine;

N-[3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenyl]-acetamide;

8-(2-Methyl-1H-indol-4-yl)-2,6-di-morpholin-4-yl-9H-purine;

3-[2-(2,6-Dimethyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purin-8-yl]-phenylamine;

N-[3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenyl]-methanesulfonamide;

{2-[2-(2,6-Dimethyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purin-8-yl]-phenyl}-methanol;

[2-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenyl]-methanol;

3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenol;
[3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenyl]-methanol;
2-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenol;
6-(3,3-Dimethyl-morpholin-4-yl)-8-(1H-indol-6-yl)-2-morpholin-4-yl-9H-purine;
6-(3,3-Dimethyl-morpholin-4-yl)-8-(1H-indol-4-yl)-2-morpholin-4-yl-9H-purine;
8-(2,3-Dihydro-1H-indol-4-yl)-2-(3-methyl-morpholin-4-yl)-6-(3-methyl-morpholin-4-yl)-9H-purine;
8-(2,3-Dihydro-1H-indol-4-yl)-2,6-bis-(3-methyl-morpholin-4-yl)-9H-purine;
8-(1H-Indol-4-yl)-2-(3-methyl-morpholin-4-yl)-6-((R)-3-methyl-morpholin-4-yl)-9H-purine;
8-(1H-Indol-6-yl)-2-(3-methyl-morpholin-4-yl)-6-((R)-3-methyl-morpholin-4-yl)-9H-purine;
8-(1H-Indol-6-yl)-2,6-bis-(3-methyl-morpholin-4-yl)-9H-purine;
8-(1H-Indol-4-yl)-6-(3-methyl-morpholin-4-yl)-2-(8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl)-9H-purine;
8-(1H-Indol-4-yl)-2-(3-methyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purine;
8-(1H-Indol-6-yl)-2-morpholin-4-yl-6-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)-9H-purine;
8-(1H-Indol-4-yl)-2-(3-methyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purine;
8-(1H-Indol-4-yl)-2-morpholin-4-yl-6-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)-9H-purine;
8-(1H-Indol-6-yl)-6-(3-methyl-morpholin-4-yl)-2-(8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl)-9H-purine;
8-(1H-Indol-4-yl)-6-(3-methyl-morpholin-4-yl)-2-(8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl)-9H-purine;
8-(1H-Indol-6-yl)-2-morpholin-4-yl-6-(3-oxa-8-aza-bicyclo[3.2.1]oct-8-yl)-9H-purine;
8-(1H-Indol-4-yl)-2-morpholin-4-yl-6-(3-oxa-8-aza-bicyclo[3.2.1]oct-8-yl)-9H-purine;
6-(1H-Indol-4-yl)-4-(3-methyl-morpholin-4-yl)-2-(3-methyl-morpholin-4-yl)-7H- pyrrolo[2,3-d]pyrimidine;
6-(1H-Indol-4-yl)-2,4-di-morpholin- 4-yl-7H-pyrrolo[2,3-d]pyrimidine;
and pharmaceutically acceptable salts thereof.

Embodiment 11: a compound according to Embodiment 1 or Embodiment 2, which is selected from:
3-[2-((2S,6R)-2,6-Dimethyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purin-8-yl]-phenol;
3-(2,4-dimorpholino-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenol;
2,6-Bis-((S)-3-methyl-morpholin-4-yl)-8-(1H-pyrrolo[2,3-b]pyridin-4-yl)-9H-purine;
{2-Fluoro-5-[6-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purin-8-yl]-phenyl}-methanol;
2-(4,4-Difluoro-piperidin-1-yl)-8-(1H-indol-4-yl)-6-((S)-3-methyl-morpholin-4-yl)-9H-purine;
5-[2,6-Bis-((S)-3-methyl-morpholin-4-yl)-9H-purin-8-yl]-1,3-dihydro-benzoimidazol-2-one;

{5-[2,6-Bis-((S)-3-methyl-morpholin-4-yl)-9H-purin-8-yl]-2-methoxy-phenyl}-methanol;
8-(1H-Indol-4-yl)-2-morpholin-4-yl-6-(8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl)-9H-purine;
2-Methoxy-5-[6-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purin-8-yl]-benzoic acid;
{4-Chloro-3-[6-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purin-8-yl]-phenyl}-methanol;
3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-benzylamine;
1-{3-[6-((S)-3-Methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purin-8-yl]-phenyl}-ethanol;
2,6-Di-morpholin-4-yl-8-(1H-pyrrolo[3,2-b]pyridin-6-yl)-9H-purine;
8-(1H-Indol-6-yl)-2,6-bis-((S)-3-methyl-morpholin-4-yl)-9H-purine;
8-(1H-Indol-4-yl)-2,6-bis-((R)-3-methyl-morpholin-4-yl)-9H-purine;
1-[8-(1H-Indol-4-yl)-6-((S)-3-methyl-morpholin-4-yl)-9H-purin-2-yl]-piperidin-4-ol;
{3-[2,6-Bis-((S)-3-methyl-morpholin-4-yl)-9H-purin-8-yl]-5-methoxy-phenyl}-methanol;
8-(1H-Indol-4-yl)-2-((R)-3-methyl-morpholin-4-yl)-6-((S)-3-methyl-morpholin-4-yl)-9H-purine;
{3-[2,6-Bis-((R)-3-methyl-morpholin-4-yl)-9H-purin-8-yl]-4-fluoro-phenyl}-methanol;
8-(1H-Indol-4-yl)-6-((R)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purine;
8-(1H-Indol-6-yl)-6-((R)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purine;
8-(1H-Indol-4-yl)-2,6-bis-((S)-3-methyl-morpholin-4-yl)-9H-purine;
8-(1H-Indol-4-yl)-6-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purine;
8-(1H-Indol-6-yl)-6-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purine;
8-(1H-Indol-4-yl)-2-(4-methoxy-piperidin-1-yl)-6-morpholin-4-yl-9H-purine;
8-(1H-Indol-4-yl)-2,6-di-morpholin-4-yl-9H-purine;
8-(1H-Indazol-4-yl)-2,6-di-morpholin-4-yl-9H-purine;
8-(1H-Indol-6-yl)-2,6-di-morpholin-4-yl-9H-purine;
3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenylamine;
N-[3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenyl]-acetamide;
8-(2-Methyl-1H-indol-4-yl)-2,6-di-morpholin-4-yl-9H-purine;
3-[2-((2S,6R)-2,6-Dimethyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purin-8-yl]-phenylamine;
N-[3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenyl]-methanesulfonamide;
{2-[2-((2S,6R)-2,6-Dimethyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purin-8-yl]-phenyl}-methanol;
[2-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenyl]-methanol;
3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenol;
[3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenyl]-methanol;
2-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenol;
3-[2-((2S,6R)-2,6-Dimethyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purin-8-yl]-phenol;

3-(2,4-dimorpholino-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenol;
2,6-Bis-((S)-3-methyl-morpholin-4-yl)-8-(1H-pyrrolo[2,3-b]pyridin-4-yl)-9H-purine;
{2-Fluoro-5-[6-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purin-8-yl]-phenyl}-methanol;
2-(4,4-Difluoro-piperidin-1-yl)-8-(1H-indol-4-yl)-6-((S)-3-methyl-morpholin-4-yl)-9H-purine;
5-[2,6-Bis-((S)-3-methyl-morpholin-4-yl)-9H-purin-8-yl]-1,3-dihydro-benzoimidazol-2-one;
{5-[2,6-Bis-((S)-3-methyl-morpholin-4-yl)-9H-purin-8-yl]-2-methoxy-phenyl}-methanol;
8-(1H-Indol-4-yl)-2-morpholin-4-yl-6-(8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl)-9H-purine;
2-Methoxy-5-[6-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purin-8-yl]-benzoic acid;
{4-Chloro-3-[6-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purin-8-yl]-phenyl}-methanol;
3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-benzylamine;
1-{3-[6-((S)-3-Methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purin-8-yl]-phenyl}-ethanol;
2,6-Di-morpholin-4-yl-8-(1H-pyrrolo[3,2-b]pyridin-6-yl)-9H-purine;
8-(1H-Indol-6-yl)-2,6-bis-((S)-3-methyl-morpholin-4-yl)-9H-purine;
8-(1H-Indol-4-yl)-2,6-bis-((R)-3-methyl-morpholin-4-yl)-9H-purine;
1-[8-(1H-Indol-4-yl)-6-((S)-3-methyl-morpholin-4-yl)-9H-purin-2-yl]-piperidin-4-ol;
{3-[2,6-Bis-((S)-3-methyl-morpholin-4-yl)-9H-purin-8-yl]-5-methoxy-phenyl}-methanol;
8-(1H-Indol-4-yl)-2-((R)-3-methyl-morpholin-4-yl)-6-((S)-3-methyl-morpholin-4-yl)-9H-purine;
{3-[2,6-Bis-((R)-3-methyl-morpholin-4-yl)-9H-purin-8-yl]-4-fluoro-phenyl}-methanol;
8-(1H-Indol-4-yl)-6-((R)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purine;
8-(1H-Indol-6-yl)-6-((R)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purine;
8-(1H-Indol-4-yl)-2,6-bis-((S)-3-methyl-morpholin-4-yl)-9H-purine;
8-(1H-Indol-4-yl)-6-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purine;
8-(1H-Indol-6-yl)-6-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purine;
8-(1H-Indol-4-yl)-2-(4-methoxy-piperidin-1-yl)-6-morpholin-4-yl-9H-purine;
8-(1H-Indol-4-yl)-2,6-di-morpholin-4-yl-9H-purine;
8-(1H-Indazol-4-yl)-2,6-di-morpholin-4-yl-9H-purine;
8-(1H-Indol-6-yl)-2,6-di-morpholin-4-yl-9H-purine;
3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenylamine;
N-[3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenyl]-acetamide;
8-(2-Methyl-1H-indol-4-yl)-2,6-di-morpholin-4-yl-9H-purine;
3-[2-((2S,6R)-2,6-Dimethyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purin-8-yl]-phenylamine;
N-[3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenyl]-methanesulfonamide;

{2-[2-((2S,6R)-2,6-Dimethyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purin-8-yl]-phenyl}-methanol;
[2-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenyl]-methanol;
3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenol;
[3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenyl]-methanol;
2-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenol;
6-(3,3-Dimethyl-morpholin-4-yl)-8-(1H-indol-6-yl)-2-morpholin-4-yl-9H-purine;
6-(3,3-Dimethyl-morpholin-4-yl)-8-(1H-indol-4-yl)-2-morpholin-4-yl-9H-purine;
8-(2,3-Dihydro-1H-indol-4-yl)-2-((S)-3-methyl-morpholin-4-yl)-6-((R)-3-methyl-morpholin-4-yl)-9H-purine;
8-(2,3-Dihydro-1H-indol-4-yl)-2,6-bis-((R)-3-methyl-morpholin-4-yl)-9H-purine;
8-(1H-Indol-4-yl)-2-((S)-3-methyl-morpholin-4-yl)-6-((R)-3-methyl-morpholin-4-yl)-9H-purine;
8-(1H-Indol-6-yl)-2-((S)-3-methyl-morpholin-4-yl)-6-((R)-3-methyl-morpholin-4-yl)-9H-purine;
8-(1H-Indol-6-yl)-2,6-bis-((R)-3-methyl-morpholin-4-yl)-9H-purine;
8-(1H-Indol-4-yl)-6-((R)-3-methyl-morpholin-4-yl)-2-(8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl)-9H-purine;
8-(1H-Indol-4-yl)-2-((R)-3-methyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purine;
8-(1H-Indol-6-yl)-2-morpholin-4-yl-6-(1S,4S)-2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl-9H-purine;
8-(1H-Indol-4-yl)-2-((S)-3-methyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purine;
8-(1H-Indol-4-yl)-2-morpholin-4-yl-6-(1S,4S)-2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl-9H-purine;
8-(1H-Indol-6-yl)-6-((S)-3-methyl-morpholin-4-yl)-2-(8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl)-9H-purine;
8-(1H-Indol-4-yl)-6-((S)-3-methyl-morpholin-4-yl)-2-(8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl)-9H-purine;
8-(1H-Indol-6-yl)-2-morpholin-4-yl-6-(3-oxa-8-aza-bicyclo[3.2.1]oct-8-yl)-9H-purine;
8-(1H-Indol-4-yl)-2-morpholin-4-yl-6-(3-oxa-8-aza-bicyclo[3.2.1]oct-8-yl)-9H-purine;
6-(1H-Indol-4-yl)-4-((R)-3-methyl-morpholin-4-yl)-2-((S)-3-methyl-morpholin-4-yl)-7H-yrrolo[2,3-d]pyrimidine;
6-(1H-Indol-4-yl)-2,4-di-morpholin- 4-yl-7H-pyrrolo[2,3-d]pyrimidine;
and pharmaceutically acceptable salts thereof.

On account of one or more than one asymmetrical carbon atom, which may be present in a compound of the formula (I), a corresponding compound of the formula (I) may exist in pure optically active form or in the form of a mixture of optical isomers, e. g. in the form of a racemic mixture. All of such pure optical isomers and all of their mixtures, including the racemic mixtures, are part of the present invention.

As used herein, the term “isomers” refers to different compounds that have the same molecular formula but differ in arrangement and configuration of the atoms. Also as used herein, the term “an optical isomer” or “a stereoisomer” refers to any of the various stereo isomeric configurations which may exist for a given compound of the present invention and includes geometric isomers. It is understood that a substituent may be attached at a chiral center of a carbon atom. The term "chiral" refers to molecules which have the property of non-superimposability on their mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner. Therefore, the invention includes enantiomers, diastereomers or racemates of the compound. “Enantiomers” are a pair of stereoisomers that are non- superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic” mixture. The term is used to designate a racemic mixture where appropriate. "Diastereoisomers” are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn- Ingold- Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either *R* or *S*. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain compounds described herein contain one or more asymmetric centers or axes and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-.

Depending on the choice of the starting materials and procedures, the compounds can be present in the form of one of the possible isomers or as mixtures thereof, for example as pure optical isomers, or as isomer mixtures, such as racemates and diastereoisomer mixtures, depending on the number of asymmetric carbon atoms. The present invention is meant to include all such possible isomers, including racemic mixtures, diasteriomeric mixtures and optically pure forms. Optically active (R)- and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a double bond, the substituent may be E or Z configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans-configuration.

It is also possible that the intermediates and compounds of the present invention may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example, proton tautomers

(also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. A specific example of a proton tautomer is the imidazole moiety where the proton may migrate between the two ring nitrogens. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

Any resulting mixtures of isomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, *e.g.*, by separation of the diastereomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. In particular, a basic moiety may thus be employed to resolve the compounds of the present invention into their optical antipodes, *e.g.*, by fractional crystallization of a salt formed with an optically active acid, *e.g.*, tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-*O,O'*-*p*-toluoyl tartaric acid, mandelic acid, malic acid or camphor-10-sulfonic acid. Racemic products can also be resolved by chiral chromatography, *e.g.*, high pressure liquid chromatography (HPLC) using a chiral adsorbent.

As used herein, the terms “salt” or “salts” refers to an acid addition or base addition salt of a compound of the invention. “Salts” include in particular “pharmaceutical acceptable salts”. The term “pharmaceutically acceptable salts” refers to salts that retain the biological effectiveness and properties of the compounds of this invention and, which typically are not biologically or otherwise undesirable. In many cases, the compounds of the present invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

In one embodiment, the invention relates to a compound of the formula (I) as defined herein, in free form. In another embodiment, the invention relates to a compound of the formula (I) as defined herein, in salt form. In another embodiment, the invention relates to a compound of the formula (I) as defined herein, in acid addition salt form. In a further embodiment, the invention relates to a compound of the formula (I) as defined herein, in pharmaceutically acceptable salt form. In yet a further embodiment, the invention relates to any one of the compounds of the Examples in free form. In yet a further embodiment, the invention relates to any one of the compounds of the Examples in salt form. In yet a further embodiment, the

invention relates to any one of the compounds of the Examples in acid addition salt form. In yet a further embodiment, the invention relates to any one of the compounds of the Examples in pharmaceutically acceptable salt form.

Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids, e.g., acetate, aspartate, benzoate, besylate, bromide/hydrobromide, bicarbonate/carbonate, bisulfate/sulfate, camphorsulfonate, chloride/hydrochloride, chlortheophyllonate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, hippurate, hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulfate, malate, maleate, malonate, mandelate, mesylate, methylsulphate, naphthoate, napsylate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, stearate, succinate, sulfosalicylate, tartrate, tosylate and trifluoroacetate salts.

Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.
Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, sulfosalicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases.

Inorganic bases from which salts can be derived include, for example, ammonium salts and metals from columns I to XII of the periodic table. In certain embodiments, the salts are derived from sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, and copper; particularly suitable salts include ammonium, potassium, sodium, calcium and magnesium salts.

Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like. Certain organic amines include isopropylamine, benzathine, cholinate, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine.

The pharmaceutically acceptable salts of the present invention can be synthesized from a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the

appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile is desirable, where practicable. Lists of additional suitable salts can be found, e.g., in “Remington's Pharmaceutical Sciences”, 20th ed., Mack Publishing Company, Easton, Pa., (1985); and in “Handbook of Pharmaceutical Salts: Properties, Selection, and Use” by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

Furthermore, the compounds of the present invention, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization. The compounds of the present invention may inherently or by design form solvates with pharmaceutically acceptable solvents (including water); therefore, it is intended that the invention embrace both solvated and unsolvated forms. The term "solvate" refers to a molecular complex of a compound of the present invention (including pharmaceutically acceptable salts thereof) with one or more solvent molecules. Such solvent molecules are those commonly used in the pharmaceutical art, which are known to be innocuous to the recipient, e.g., water, ethanol, and the like. The term "hydrate" refers to the complex where the solvent molecule is water.

Compounds of the invention, i.e. compounds of formula (I) that contain groups capable of acting as donors and/or acceptors for hydrogen bonds may be capable of forming co-crystals with suitable co-crystal formers. These co-crystals may be prepared from compounds of formula (I) by known co-crystal forming procedures. Such procedures include grinding, heating, co-subliming, co-melting, or contacting in solution compounds of formula (I) with the co-crystal former under crystallization conditions and isolating co-crystals thereby formed. Suitable co-crystal formers include those described in WO 2004/078163. Hence the invention further provides co-crystals comprising a compound of formula (I).

The compounds of the present invention, including salts, hydrates and solvates thereof, may inherently or by design form polymorphs.

Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into

compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F ^{31}P, ^{32}P, ^{35}S, ^{36}Cl, ^{125}I respectively. The invention includes various isotopically labeled compounds as defined herein, for example those into which radioactive isotopes, such as ^{3}H and ^{14}C, or those into which non-radioactive isotopes, such as ^{2}H and ^{13}C are present. Such isotopically labelled compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^{2}H or ^{3}H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or labeled compound may be particularly desirable for PET or SPECT studies. Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

Further, substitution with heavier isotopes, particularly deuterium (i.e., ^{2}H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent of a compound of the formula (I). The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this invention is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_2O, d_6-acetone, d_6-DMSO.

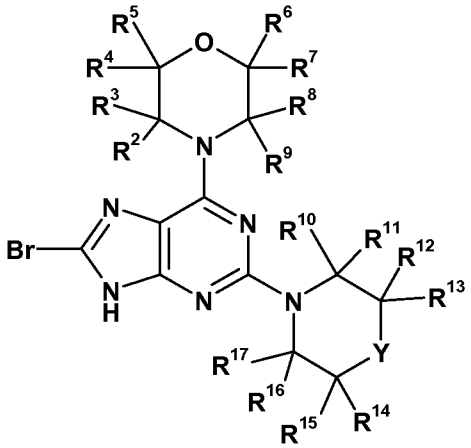
Compounds of the present invention may be synthesized by synthetic routes that include processes analogous to those well-known in the chemical arts, particularly in light of the description contained herein. The starting materials are generally available from commercial

sources such as Aldrich Chemicals (Milwaukee, Wis.) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, Reagents for Organic Synthesis, v. 1-19, Wiley, New York (1967-1999 ed.), or Beilsteins Handbuch der organischen Chemie, 4, Aufl. ed. Springer-Verlag, Berlin, including supplements (also available via the Beilstein online database)).

For illustrative purposes, the reaction schemes depicted below provide potential routes for synthesizing the compounds of the present invention as well as key intermediates. For a more detailed description of the individual reaction steps, see the Examples section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the inventive compounds. Although specific starting materials and reagents are depicted in the schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

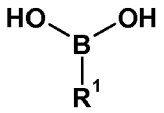
In a further aspect, the invention relates to a process for the preparation of a compound of the formula (I), in free form or in pharmaceutically acceptable salt form, comprising

(a) when X represents N in a compound of formula (I), the reaction of a compound of formula (IIa)

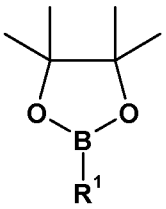


(IIa)

in which R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} are as defined for formula (I), with a compound of formula (III) or (IV)



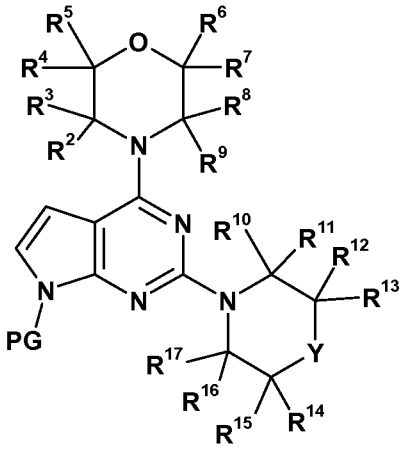
(III)



(IV)

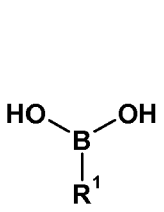
in which R^1 is as defined for formula (I), or

b) when X represents CH in a compound of formula (I), the reaction of a compound of formula (IIb)

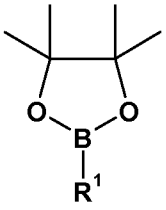


(IIb)

in which R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} are as defined for formula (I) and PG is a protecting group, with a compound of formula (III) or (IV)



(III)



(IV)

in which R^1 is as defined for formula (I),

and thereafter

i) the optional reduction, oxidation or other functionalisation of the resulting compound,

ii) the cleavage of any protecting group(s) present,

iii) the recovery of the so obtainable compound of the formula (I) in free form or in pharmaceutically acceptable salt form, and/or

iv) the optional separation of mixtures of optically active isomers into their individual optically active isomeric forms.

The reactions can be effected according to conventional methods. For example, the reaction described in step (a) above may be carried out in the presence of a suitable metal catalyst, for example tetrakis(triphenylphosphine)palladium, a suitable base, for example cesium fluoride, a suitable solvent, for example acetonitrile/water and at a suitable temperature, for example 50 to 150°C, more suitably 90 to 130°C.

The reaction described in step (b) above may be carried out in the presence of a suitable catalyst, for example palladium (II) acetate, a suitable oxidant, for example copper (II) acetate, a suitable solvent, for example acetic acid, and at a suitable temperature, for example 0 to 50°C, or more suitably room temperature.

Within the scope of this text, only a readily removable group that is not a constituent of the particular desired end product of the compounds of the present invention is designated a "protecting group", unless the context indicates otherwise. The protection of functional groups by such protecting groups, the protecting groups themselves, and their cleavage reactions are described for example in standard reference works, such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981, in "Methoden der organischen Chemie" (Methods of Organic Chemistry), Houben Weyl, 4th edition, Volume 15/I, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jeschkeit, "Aminosäuren, Peptide, Proteine" (Amino acids, Peptides, Proteins), Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (Chemistry of Carbohydrates: Monosaccharides and Derivatives), Georg Thieme Verlag, Stuttgart 1974. A characteristic of protecting groups is that they can be removed readily (i.e. without the occurrence of undesired secondary reactions) for example by solvolysis, reduction, photolysis or alternatively under physiological conditions (*e.g.* by enzymatic cleavage).

Salts of compounds of the present invention having at least one salt-forming group may be prepared in a manner known to those skilled in the art. For example, salts of compounds of the present invention having acid groups may be formed, for example, by treating the compounds with metal compounds, such as alkali metal salts of suitable organic carboxylic acids, *e.g.* the sodium salt of 2-ethylhexanoic acid, with organic alkali metal or alkaline earth metal compounds, such as the corresponding hydroxides, carbonates or hydrogen carbonates, such as sodium or potassium hydroxide, carbonate or hydrogen carbonate, with

corresponding calcium compounds or with ammonia or a suitable organic amine, stoichiometric amounts or only a small excess of the salt-forming agent preferably being used. Acid addition salts of compounds of the present invention are obtained in customary manner, *e.g.* by treating the compounds with an acid or a suitable anion exchange reagent. Internal salts of compounds of the present invention containing acid and basic salt-forming groups, *e.g.* a free carboxy group and a free amino group, may be formed, *e.g.* by the neutralisation of salts, such as acid addition salts, to the isoelectric point, *e.g.* with weak bases, or by treatment with ion exchangers.

Salts can be converted into the free compounds in accordance with methods known to those skilled in the art. Metal and ammonium salts can be converted, for example, by treatment with suitable acids, and acid addition salts, for example, by treatment with a suitable basic agent.

For those compounds containing an asymmetric carbon atom, the compounds exist in individual optically active isomeric forms or as mixtures thereof, e.g. as racemic or diastereomeric mixtures. The present invention embraces both individual optically active R and S isomers as well as mixtures, e.g. racemic or diastereomeric mixtures, thereof. In addition, the present invention embraces all geometric and positional isomers. For example, if a compound of the present invention incorporates a double bond or a fused ring, both the *cis*- and *trans*- forms, as well as mixtures, are embraced within the scope of the invention.

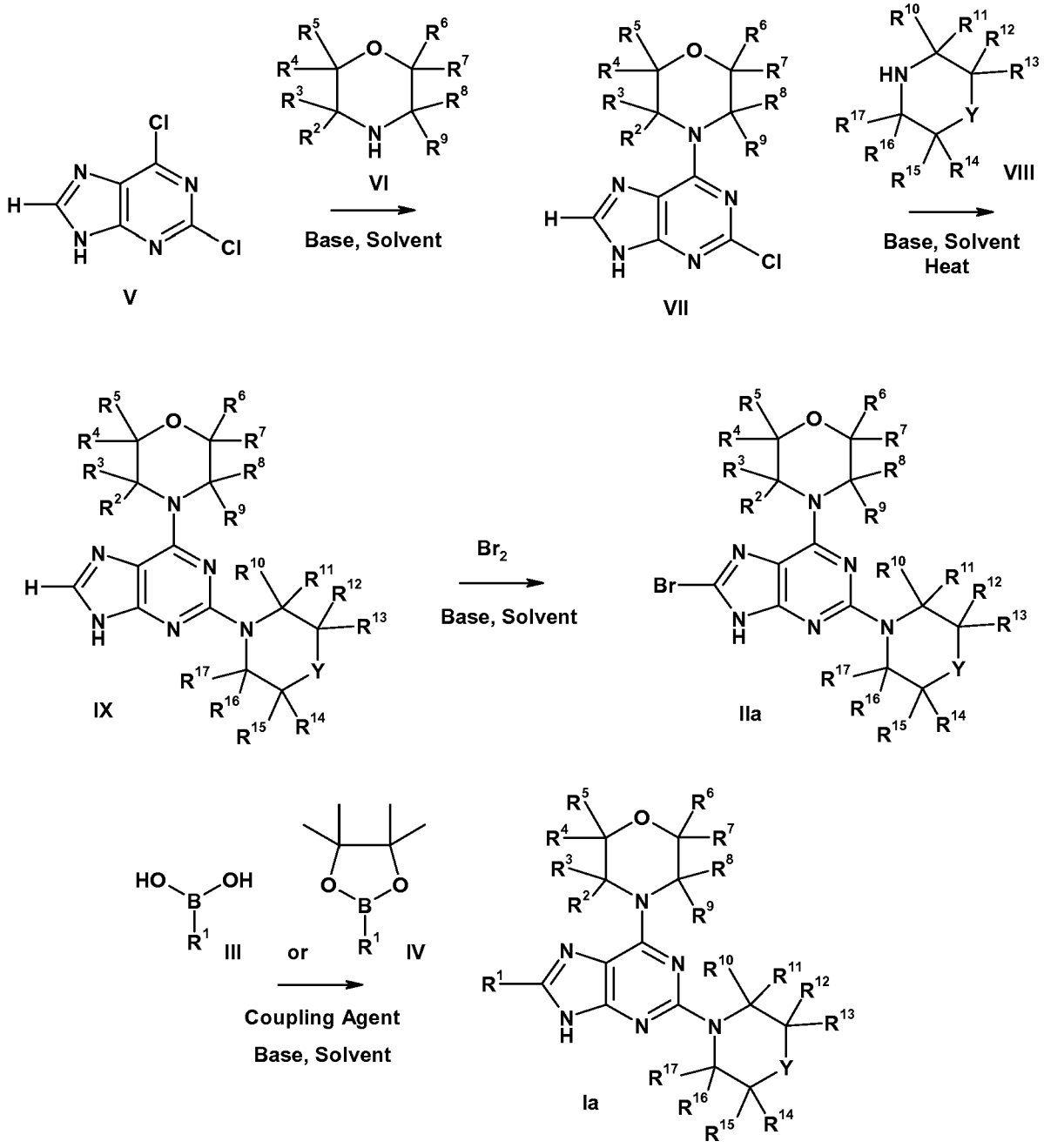
Diastereomeric mixtures can be separated into their individual diastereoisomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereoisomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Also, some of the compounds of the present invention may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of a commercially available chiral HPLC column.

The invention further includes any variant of the present processes, in which an intermediate product obtainable at any stage thereof is used as starting material and the remaining steps are carried out, or in which the starting materials are formed *in situ* under the reaction conditions, or in which the reaction components are used in the form of their salts or optically

pure material. Compounds of the invention and intermediates can also be converted into each other according to methods generally known to those skilled in the art.

For illustrative purposes, the reaction schemes depicted below provide potential routes for synthesizing the compounds of the present invention as well as key intermediates. For a more detailed description of the individual reaction steps, see the Examples section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the inventive compounds. Although specific starting materials and reagents are depicted in the schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

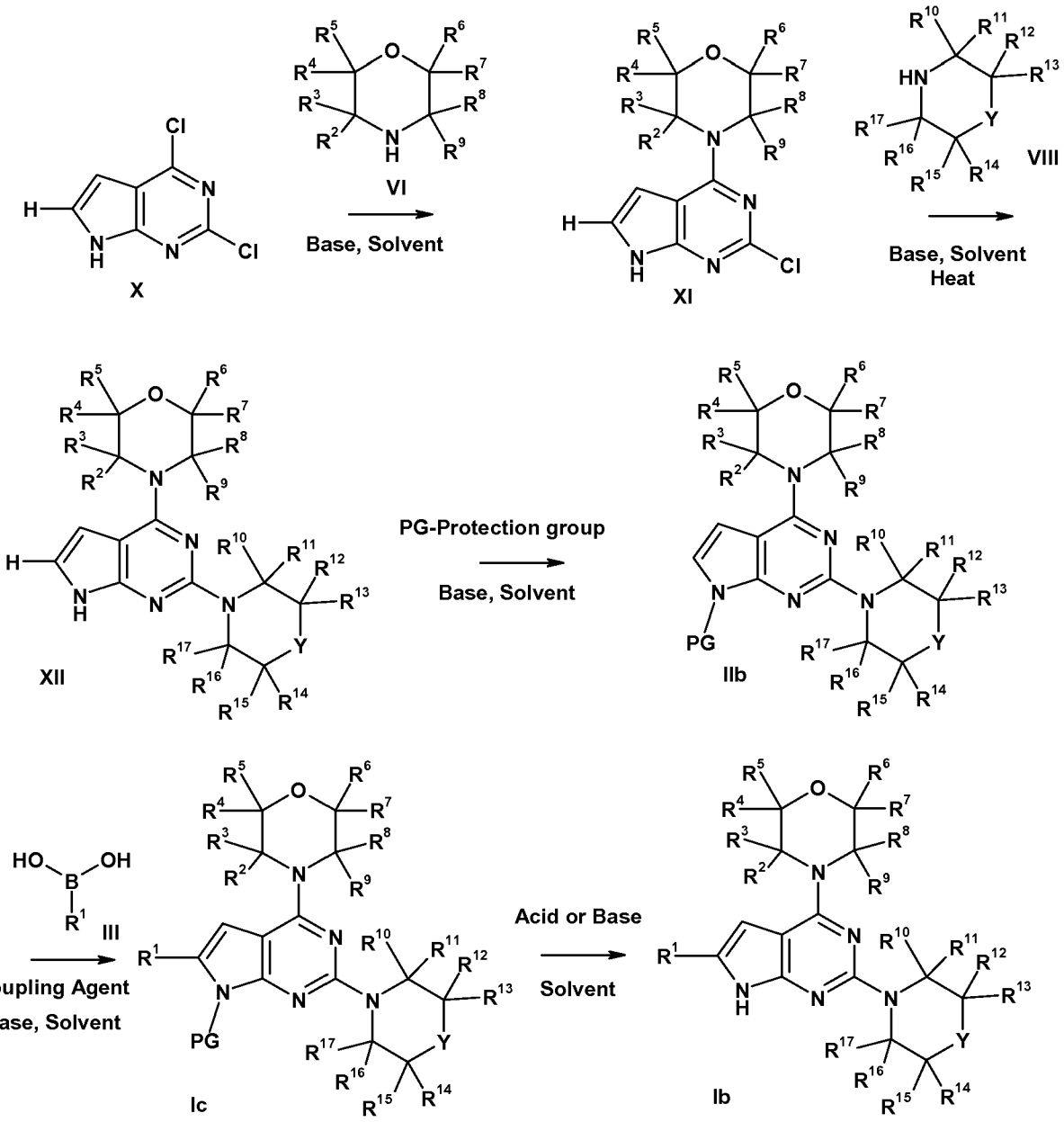
Scheme 1. General Procedure 1 for synthesis of purine compounds



Generally, the compounds of formula **Ia** can be prepared according to Scheme 1 in four steps, starting from commercially available intermediate **V**. As to the individual steps in the scheme shown above, step one involves preparation of the intermediate **VII** by chlorine displacement with nucleophile such as functionalized morpholino intermediate **VI**. Intermediate **IX** can be prepared by reaction of intermediate **VII** with intermediate **VIII** in presence of adequate base such as diisopropylethyl amine, solvent such as dimethyl acetamide and heat . Step three involves bromination of the intermediate **IX** to intermediate **IIa** that can be done utilizing bromine in appropriate solvent such as dichloromethane.

Target compounds of structure **Ia** can be prepared by coupling of intermediate **II** with variety of commercially available or synthesized boronic acids or esters of structure **III or IV** using metal catalysts most often exemplified by commercially available palladium complexes.

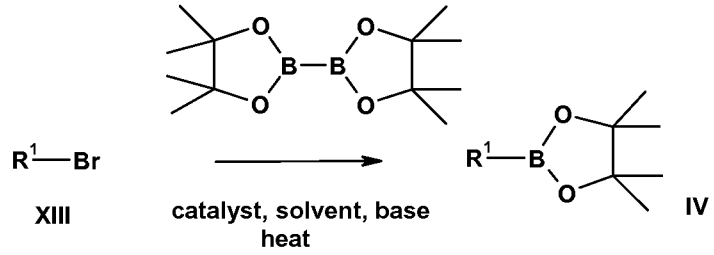
Scheme 2. General procedure for synthesis of pyrrolo pyrimidine compounds



Generally, the compounds of formula **Ib** can be prepared according to Scheme 2 in five steps, starting from commercially available intermediate **X**. As to the individual steps in the Scheme 2, step one involves preparation of intermediate **XI** by chlorine displacement with nucleophile such as functionalized morpholino intermediate **VI**. Intermediate **XII** can be prepared by reacting intermediate **XI** with intermediate **VIII** in the presence of solvent such as

dimethyl acetamide, base such as diisopropylethyl amine and heat. Step three involves protection of intermediate **XII** to intermediate **IIb** using adequate protection group such as benzylchloride or SEM-Chloride in the presence of base such as sodium hydride and solvent such as tetrahydrofuran. Step four involves coupling of intermediate **IIb** with adequate boronic acid in presence of adequate solvent such as acetic acid, oxidant such as copper acetate and commercially available palladium catalyst. Final step to target compounds exemplified by structure **Ib** involve the removal of the protection group using acid base or adequate catalysts such as palladium.

Scheme 3. General Procedure for synthesis of boronic esters.



Boronic esters of formula **IV** can be prepared according to Scheme 3 in one step where R^1 is as described in formula (I). The step involves reacting substituted arylbromide or heteroarylbromide of formula **XIII** with bis(pinacolato)diboron in the presence of commercially available palladium catalyst, solvent such as dioxane at temperature ranging from 80°C to 120°C.

Compounds of the formula (I), in free form or in pharmaceutically acceptable salt form, hereinafter often referred to as "agents of the invention", exhibit valuable pharmacological properties, when tested *in vitro*, and may, therefore, be useful in medicaments, in therapy or for use as research chemicals, for example as tool compounds.

The agents of the invention are inhibitors of class I PI3Ks and mTOR. The inhibiting properties of a compound of the invention towards class I PI3Ks and mTOR can be evaluated in tests as described hereinafter.

Biological Assays

Test 1: PI3 Kinase Assay

PI3K KinaseGlo assay: 50 nL of compound dilutions were dispensed onto black 384-well low volume Non Binding Styrene (NBS) plates (Costar Cat. No. NBS#3676). L-a-phosphatidylinositol (PI), provided as 10 mg/ml solution in methanol, was transferred into a

glass tube and dried under nitrogen beam. It was then resuspended in 3% OctylGlucoside (OG) by vortexing and stored at 4°C. The KinaseGlo Luminescent Kinase Assay (Promega, Madison/WI, USA) is a homogeneous HTS method of measuring kinase activity by quantifying the amount of ATP remaining in solution following a kinase reaction.

5 µL of a mix of PI/OG with the PI3K subtype were added (Table 1). Kinase reactions were started by addition of 5 µl of ATP-mix containing in a final volume 10 µL 10 mM TRIS-HCl pH 7.5, 3mM $MgCl_2$, 50 mM NaCl, 0.05% CHAPS, 1mM DTT and 1 µM ATP, and occurred at room temperature. Reactions were stopped with 10 µl of KinaseGlo and plates were read 10 mins later in a Synergy2 reader using an integration time of 0.1 seconds per well. 2.5 µM of a pan-class 1 PI3 kinase inhibitor (standard) was added to the assay plates to generate the 100% inhibition of the kinase reaction, and the 0% inhibition was given by the solvent vehicle (90% DMSO in water). The standard was used as a reference compound and included in all assay plates in the form of 16 dilution points in duplicate.

Cloning of PI3Ks

The PI3Kα construct is a fusion of p85α iSH2 domain and the respective p110 isoform. The p85α fragment and p110 isoform gene were generated by PCR from first strand cDNA generated by RT-PCR from commercial RNA from placenta, testis and brain as described below.

PI3Kα constructs and proteins

BV1075: The construct for Baculovirus BV-1075 was generated by a three-part ligation comprised of a p85 fragment and a p110α fragment cloned into vector pBlueBac4.5. The p85 fragment was derived from plasmid p1661-2 digested with Nhe/Spe. The p110α fragment derived from its clone was verified by sequencing and used in LR410 as a SpeI/HindIII fragment. For the generation of the baculovirus expression vector LR410 the gateway LR reaction to transfer the insert into the Gateway adapted pBlueBac4.5 (Invitrogen) vector was used. The cloning vector pBlueBac4.5 (Invitrogen) was digested with Nhe/HindIII. This resulted in the construct PED 153.8. The p85 component (iSH2) was generated by PCR using ORF 318 as a template and one forward primer KAC1028 (5'-gctagcatgcgagaatatgatagat-tatatgaag-aatatacc) (SEQ ID NO: 1) and two reverse primers, KAC1029 (5'-gcctccaccac-ctccgcctg-gtttaatgctgttcatacgtttgtc) (SEQ ID NO: 2) and KAC1039 (5'- tactagtc-cgcctccac-cacctccgcctccaccacctccgcc) (SEQ ID NO: 3). The two reverse primers overlap and incorporate a 12x Gly linker and the N-terminal sequence of the p110α gene to the SpeI site. The PCR fragment was cloned into pCR2.1 TOPO (Invitrogen). Of the resulting clones, p1661-2 was determined to be correct by sequencing. This plasmid was

digested with Nhe and SpeI and the resulting fragment was gel-isolated and purified for sub-cloning.

The p110α cloning fragment was generated by enzymatic digest of clone LR410 (see above) with Spe I and HindIII. The SpeI site is in the coding region of the p110α gene. The resulting fragment was gel-isolated and purified for sub-cloning. The cloning vector, pBlueBac4.5 (Invitrogen) was prepared by enzymatic digestion with Nhe and HindIII. The cut vector was purified with Qiagen column and then dephosphorylated with Calf Intestine alkaline phosphatase (CIP) (BioLabs). After completion of the CIP reaction the cut vector was again column purified to generate the final vector. A three-part ligation was performed using Roche Rapid ligase and the vendor specifications. The final plasmid was verified by sequencing.

Protein sequence of BV 1075 (SEQ ID NO: 4):

```
   1 MREYDRLYEE YTRTSQEIQM KRTAIEAFNE TIKIFEEQCQ TQERYSKEYI EKFKREGNEK
  61 EIQRIMHNYD KLKSRISEII DSRRRLEEDL KKQAAEYREI DKRMNSIKPG GGGGGGGGGG
 121 GLVECLLPNG MIVTLECLRE ATLITIKHEL FKEARKYPLH QLLQDESSYI FVSVTQEAER
 181 EEFFDETRRL CDLRLFQPFL KVIEPVGNRE EKILNREIGF AIGMPVCEFD MVKDPEVQDF
 241 RRNILNVCKE AVDLRDLNSP HSRAMYVYPP NVESSPELPK HIYNKLDKGQ IIVVIWVIVS
 301 PNNDKQKYTL KINHDCVPEQ VIAEAIRKKT RSMLLSSEQL KLCVLEYQGK YILKVCGCDE
 361 YFLEKYPLSQ YKYIRSCIML GRMPNLMLMA KESLYSQLPM DCFTMPSYSR RISTATPYMN
 421 GETSTKSLWV INSALRIKIL CATYVNVNIR DIDKIYVRTG IYHGGEPLCD NVNTQRVPCS
 481 NPRWNEWLNY DIYIPDLPRA ARLCLSICSV KGRKGAKEEH CPLAWGNINL FDYTDTLVSG
 541 KMALNLWPVP HGLEDLLNPI GVTGSNPNKE TPCLELEFDW FSSVVKFPDM SVIEEHANWS
 601 VSREAGFSYS HAGLSNRLAR DNELRENDKE QLKAISTRDP LSEITEQEKD FLWSHRHYCV
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 901 IFKNGDDLRQ DMLTLQIIRI MENIWQNQGL DLRMLPYGCL SIGDCVGLIE VVRNSHTIMQ
 961 IQCKGGLKGA LQFNSHTLHQ WLKDKNKGEI YDAAIDLFTR SCAGYCVATF ILGIGDRHNS
1021 NIMVKDDGQL FHIDFGHFLD HKKKKFGYKR ERVPFVLTQD FLIVISKGAQ ECTKTREFER
1081 FQEMCYKAYL AIRQHANLFI NLFSMMLGSG MPELQSFDDI AYIRKTLALD KTEQEALEYF
1141 MKQMNDAHHG GWTTKMDWIF HTIKQHALNE LGGAHHHHHH (SEQ ID NO: 4)
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Purification of PI3Kα constructs

PI3Kα was purified in two chromatographic steps: immobilized metal affinity chromatography (IMAC) on a Ni sepharose resin (GE Healthcare) and gel filtration utilizing a Superdex 200 26/60 column (GE Healthcare). All buffers were chilled to 4ºC and lysis was performed chilled on ice. Column fractionation was performed at room temperature.

Typically frozen cells from 10 L of Tn5 cell culture were resuspended in "Lysis Buffer" 20 mM Tris-Cl, pH 7.5, 500 mM NaCl, 5% glycerol, 5 mM imidazole, 1 mM NaF, 0.1ug/mL okadaic acid (OAA), 5 mM BME, 1 x Complete protease inhibitor cocktail – EDTA-free (20 tablets/1 L buffer, Roche Applied Sciences), benzonase (25U/mL buffer, EMD Biosciences) at a ratio of 1:6 v/v pellet to Lysis Buffer ratio, and mechanically lysed by douncing for 20 strokes using a tight-fitting pestle. The lysate was centrifuged at 45,000 g for 30 minutes, and the supernatant was loaded onto a pre-equilibrated IMAC column (3 mL resin/100 mL lysate). The column was washed with 3-5 column volumes of Lysis Buffer, followed by a second wash of 3-5 column volumes with 20 mM Tris-Cl, pH 7.5, 500 mM NaCl, 5% glycerol, 45 mM imidazole, 1 mM NaF, 0.1µg/mL OAA, 5 mM BME, 1x Complete protease inhibitor cocktail – EDTA-free. Protein was eluted with 20 mM Tris-Cl, pH 7.5, 0.5 M NaCl, 5% glycerol, 250 mM imidazole, 1 mM NaF, 0.1µg/mL OAA, 5 mM BME, 1x Complete protease inhibitor cocktail – EDTA-free. Pertinent fractions were analyzed by SDS-PAGE and pooled accordingly. The protein was further purified by gel filtration on a Superdex 200 26/60 column equilibrated in 20 mM Tris-Cl, pH 7.5, 0.5 M NaCl, 5% glycerol, 1 mM NaF, 5 mM DTT, 1x Complete protease inhibitor cocktail – EDTA-free. Pertinent fractions were analyzed by SDS-PAGE and pooled accordingly. An equal volume of Dialysis Buffer (20 mM Tris-Cl, pH 7.5, 500 mM NaCl, 50% glycerol, 5 mM NaF, 5 mM DTT) was added to the pool and than dialyzed against Dialysis Buffer two changes (one change overnight). Protein was stored at -20°C.

Test 2: mTOR biochemical assay

IC50s for mTOR interacting compounds were assessed using the FRAP1/mTOR TR-FRET tracer assay (Invitrogen by Life Technologies). FRAP1/mTOR (PV4753) and LanthaScreen Eu-Anti-GST Antibody (PV5594) (total volume of 14 µL) were added to each well of a ProxiPlate-384 Plus (Perkin-Elmer) 384-well plate. Compounds were serially diluted in DMSO (12-point, 4X dilution factor) and 1 µL of diluted compound was then added to each well and mixed by pipetting using a Biomek FX (Beckman Coulter). 5 µL of mTOR Kinase Tracer 314 (PV6087) was added to each well, mixed and plates were incubated at room temperature for 1 hour. Final concentrations of components are: 6 nM FRAP1/3 nM LanthaScreen Eu-Anti-GST Antibody/50 nM mTOR Kinase Tracer 314/unlabeled compounds, $4.8*10^{\wedge-6}$-20µM. Final assay buffer composition is: 50 mM HEPES (pH 7.5), 50 mM NaCl, 5 mM $MgCl_2$, 1 mM EGTA, 0.01% Pluronic F-127. Plates were measured in plate reader (Perkin Elmer, EnVision) using 340 nm excitation and emission at two wavelengths, Emission-1 665 nm and Emission-2 615 nm. The TR-FRET ratio for each well (Emission-1

665/Emission-2 615) was plotted against compound concentration using GraphPad Prism software and IC50s were determined using nonlinear regression with outlier elimination.

Test 3: TSC Assay

The following is a description of a high content imaging assay, utilizing TSC1-/- mouse embryonic fibroblasts (MEFs) cells, to test compounds for the inhibition of a constitutively active mTOR. The assay is based on the staining of phospho-S6 (240/244) using a commercially available antibody and detection with a fluorescently labeled secondary antibody. This assay generates IC50 values for compounds that inhibit mTOR. Here is described an imaging protocol and image recognition algorithm to visualize and measure changes in pS6 240/244 levels.

Quantification of pS6 staining using high-content imaging and analysis

1. Day 0: Cell plating. Subconfluent TSC1-/- MEFs are harvested by trypsinization, resuspended in growth medium, and counted. A cell suspension of 166`666 cells/mL is prepared and 30 µL is added into the wells of a 384-well plate using an electronic multichannel pipette. This results in 5000 cells/well being plated. The plates are briefly spun down and placed at 37°C and 5% CO_2.
2. Day 1: Cell plates are washed into a PBS starve solution (contains glucose, sodium bicarbonate, HEPES and phenol red) using a 384-well plate washer. The wash protocol aspirates the volume down to 30 µL/well before dispensing 60 µL/well of the PBS starve solution. Aspiration and dispensing steps are repeated 8 times and a final volume of 30 µL/well is left. The cell plates are placed at 37°C and 5% CO_2 for 2hrs.
   Compound treatment. Compound dose responses are prepared in DMSO. The dose responses are then diluted 1:50 in medium. 10ul of the diluted compound is added to 30ul of cells, yielding a final 1:200 dilution of the original compound and final of 0.5% DMSO. Compound-treatments are performed in triplicates. The plates are placed at 37°C and 5% CO_2 for 2hrs.. Cells are then fixed by adding 10 µL/well 5x concentrated Mirsky`s fixative. This results in a total volume of 50µL per well and a concentration of 1x Mirsky`s fixative. The cell plates are briefly spun down and incubated for 1 h at room temperature. Cells are then washed using a 384-well plate washer using a protocol which aspirates the volume down to 30 µL/well before dispensing 60 µL/well 1X TBS. Aspiration and dispensing steps are repeated 8 times and then an additional aspiration step leaves a final volume of 10 µL/well. Block buffer (1X TBS + 0.1% Triton X-100 + 0.1% BSA) is then added at 25 µL/well and the plates are incubated at room

temperature for 30min.. The cell plates are then aspirated down to 10 µL/well. Primary antibody (Phospho-S6 Ribosomal Protein (Ser240/244) (61H9) Rabbit mAb Cell Signaling #4838) is diluted 1:150 in block buffer and then 10 µL/well is added to the cell plates. Plates are incubated overnight at 4°C.

3. Day 2: Cell plates are washed using 1X TBS method detailed above and then a secondary antibody solution is added at 10 µL/well (secondary antibody solution: block buffer + Hoechst 10ug/ml + goat anti-rabbit Cy5 secondary (diluted 1:150))(Goat anti-rabbit IgG Cy5: Chemicon International #AP187 / Hoechst 33342: Invitrogen #H3570). Plates are incubated for 1hr at room temperature and then washed with 1X TBS using the protocol detailed above without the final aspiration step which results in a final volume of 90 µL TBS/well .

   Imaging. The bottom of the plate is cleaned with 70% ethanol and then imaged using the InCell 1000 automated epifluorescence microscope. 10x magnification is used and 1 area (field) is imaged per well, this typically captures a total of around 400 cells per well. Hoechst33342 images are acquired using an excitation of 360 nm (D360_40x filter), an emission of 460 nM (HQ460_40M filter) and an exposure time of 200 ms. Cy5 images are acquired using an excitation of 620 nm (Chroma 620_60X filter), an emission of 700 nM (Chroma HQ700_75M filter) and an exposure time of 200ms. A double band pass mirror is used for all images.

4. Image analysis: The InCell Analysis software is used to analyze the images using the Dual Object algorithm. First, nuclei are detected in the Hoechst33342 image using top-hat segmentation and a minimal nuclear area of 10µm^2. Second, cells are defined using a collar of 0.7 µm around the nuclei. The Cy5 fluorescence intensity inside the collar is measured (cell intensity) and results are reported on an “Average per cell” basis.
5. IC50 calculation: IC50s are calculated by plotting the cell intensity values on the y-axis with dose response values on the x-axis. IC50 values represent compound potency against mTOR.

Test 4: Autophagy assay

Autophagy is a catabolic pathway that degrades bulk cytosol in lysosomal compartments enabling amino acids and fatty acids to be recycled. One of the key regulators of autophagy is the mammalian target of rapamycin (mTOR), a conserved serine/threonine kinase which suppresses the initiation of the autophagic process when nutrients, growth factors and energy are available. To quantify autophagy induction by mTOR inhibitors, we use a mCherry-GFP-LC3 reporter which is amenable to retroviral delivery into mammalian cells, stable expression and analysis by fluorescence microscopy.

mCherry-GFP-LC3 Reporter

The amino acid sequence of the mCherry-GFP-LC3 construct is shown below (SEQ ID NO: 5). The mCherry sequence is underlined, GFP sequence is in bold and LC3A sequence is boxed.

MVSKGEEDNMAIIKEFMRFKVHMEGSVNGHEFEIEGEGEGRPYEGTQTAK
LKVTKGGPLPFAWDILSPQFMYGSKAYVKHPADIPDYLKLSFPEGFKWER
VMNFEDGGVVTVTQDSSLQDGEFIYKVKLRGTNFPSDGPVMQKKTMGWEA
SSERMYPEDGALKGEIKQRLKLKDGGHYDAEVKTTYKAKKPVQLPGAYNV
NIKLDITSHNEDYTIVEQYERAEGRHSTGGMDELYKPVAT**MVSKGEELFT**
GVVPILVELDGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLPVPWPT
LVTTLTYGVQCFSRYPDHMKQHDFFKSAMPEGYVQERTIFFKDDGNYKTR
AEVKFEGDTLVNRIELKGIDFKEDGNILGHKLEYNYNSHNVYIMADKQKN
GIKVNFKIRHNIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALSK
DPNEKRDHMVLLEFVTAAGITLGMDELYKSGLRSRAQASNSAVDMPSDRP
FKQRRSFADRCKEVQQIRDQHPSKIPVIIERYKGEKQLPVLDKTKFLVPD
HVNMSELVKIIRRRLQLNPTQAFFLLVNQHSMVSVSTPIADIYEQEKDED
GFLYMVYASQETFGF

Described hereinafter is an imaging protocol and image recognition algorithm to visualize and measure changes in the autophagic pathway.

Quantification of autophagy using high-content imaging and analysis

1. Day 0: Cell plating. Subconfluent H4 mCherry-GFP-LC3 cells are harvested by trypsinization, resuspended in growth medium, and counted (H4 cells: Human neuroglioma cell line (ATCC)). A cell suspension of 66`000 cells/mL is prepared and 30 µL are added into the wells of a 384-well plate using an electronic multichannel pipette.

This results in 2000 cells/well being plated. The cell plates are briefly spun down and placed at 37ºC and 5% CO_2.

2. Day 1: Compound treatment. Compound dose responses are prepared in DMSO. The dose responses are then diluted 1:50 in medium. 10ul of the diluted compound is added to 30ul of cells, yielding a final 1:200 dilution of the original compound and final of 0.5% DMSO. Compound-treatments are performed in triplicates. The 384-well plates are placed at 37ºC and 5% CO_2. Compound treatment is performed for 16-18 h (see Note 1).
3. Day 2: Cell fixation. Cells are fixed by adding 10 µL/well 5x concentrated Mirsky`s fixative supplemented with 25µg/mL Hoechst33342. This results in a total volume of 50µL per well and a concentration of 1x Mirsky`s fixative and 5 µg/mL Hoechst33342. The 384-well plate is briefly spun down and incubated for 1 h at room temperature. Cells are then washed using a 384-well plate washer using a protocol which aspirates the volume down to 10 µL/well before dispensing 100 µL/well 1X TBS. Aspiration and dispensing steps are repeated 4 times and a final volume of 100 µL/well is left. The plate is sealed using an adhesive PCR foil.
4. Imaging. The bottom of the plate is cleaned with 70% ethanol and then imaged using the InCell 1000 automated epifluorescence microscope. 20x magnification is used and 4 different areas (fields) are imaged per well, this typically captures a total of around 400 cells per well. Hoechst33342 images are acquired using an excitation of 360 nm (D360_40x filter), an emission of 460 nM (HQ460_40M filter) and an exposure time of 150 ms. GFP images are acquired using an excitation of 475 nm (S475_20x filter), an emission of 535 nM (HQ535_50M filter) and an exposure time of 1 s. mCherry images are acquired using an excitation of 535 nm (HQ535_50x filter), an emission of 620 nM (HQ620_60M filter) and an exposure time of 1 s. A quadruple band pass mirror is used for all images.
5. Image analysis. The InCell Analysis software is used to analyze the images using the Multi Target Analysis algorithm. First, nuclei are detected in the Hoechst33342 image using top-hat segmentation and a minimal nuclear area of 50µm^2. Cells are defined using a collar of 10 µm around the nuclei. Second, puncta (organelles) are identified in the mCherry image inside the cells using multi-top-hat segmentation. Third, the mask of the mCherry puncta is transferred onto the GFP image. Fourth, the GFP fluorescence intensity inside the mCherry puncta mask is measured (reference intensity).
6. The `organelles` parameter reflects mCherry-positive puncta of the mCherry-GFP-LC3 reporter and is used to calculate `LC3 puncta/cell'. For this purpose, the number of organelles is calculated per cell and averaged over all the cells in a given well (average per cell basis). mCherry-positive LC3 puncta numbers (y-axis) are plotted against the compound dose response values (x-axis) and EC50 values are calculated for each

compound. EC50 values represent compound potency in terms of autophagy activation (e.g. increase in mCherry-positive LC3 puncta count).

Notes

1. Autophagy-modulation and redistribution of mCherry-GFP-LC3 can be already observed after a compound treatment time of 3-4 h. However, more robust effects are seen with 16-18 h treatment times.

The compounds of the Examples showed the values presented in Table 1 below when tested in the above assays.

Table 1

Example Number	Test 1: PI3Kα IC_{50} (nM)	Test 2: mTOR IC_{50} (nM)	Test 3: TSC1-/- IC_{50} (nM)	Test 4: Autophagy EC_{50} (nM)
1	20	NT	118	NT
2	1059	40	300	363
3	6530	510	2320	> 2000
4	1800	1424	1865	1551
5	>9100	150	551	2594
6	>9100	30	1452	NT
7	2540	NT	455	NT
8	>9100	41	127	731
9	>9100	3204	7300	> 10000
10	720	1836	5718	> 10000
11	8140	2425	6016	> 2000
12	2870	2023	1964	> 10000
13	430	469	2783	8529
14	>9100	7	349	1284
15	4580	9	62	1781
16	7300	160	460	2000
17	400	399	1511	3193
18	5050	46	70	2500
19	170	134	300	2000
20	6050	6	90	452
21	>9100	237	831	498
22	5860	5	113	761

23	5510	14	138	1610
24	8540	85	632	NT
25	2070	172	452	> 700
26	570	8	81	184
27	40	340	7186	5934
28	9050	372	458	> 200
29	3860	1208	2085	> 5000
30	3010	1447	1515	> 2000
31	590	NT	315	NT
32	2520	1044	1035	NT
33	>9100	380	2987	7733
34	>9100	NT	8002	NT
35	5870	NT	4006	NT
36	20	NT	73	NT
37	10	NT	620	NT
38	480	NT	>50000	NT

NT = Not Tested

As used herein, the term "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (*e.g.*, antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drugs, drug stabilizers, binders, excipients, disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, and the like and combinations thereof, as would be known to those skilled in the art (see, for example, Remington's Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, pp. 1289- 1329). Except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated.

The term "a therapeutically effective amount" of a compound of the present invention refers to an amount of the compound of the present invention that will elicit the biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease, etc. In one non-limiting embodiment, the term “a therapeutically effective amount” refers to the amount of the compound of the present invention that, when administered to a subject, is effective to (1) at least partially alleviating, inhibiting, preventing and/or ameliorating a condition, or a disorder or a disease (i) mediated by class I PI3K and/or

mTOR or (ii) associated with class I PI3K and/or mTOR activity, or (iii) characterized by activity (normal or abnormal) of class I PI3K and/or mTOR; or (2) reducing or inhibiting the activity of class I PI3K and/or mTOR. In another non-limiting embodiment, the term "a therapeutically effective amount" refers to the amount of the compound of the present invention that, when administered to a cell, or a tissue, or a non-cellular biological material, or a medium, is effective to at least partially reduce or inhibit the activity of class I PI3K and/or mTOR. The meaning of the term "a therapeutically effective amount" as illustrated in the above embodiments for class I PI3K and/or mTOR also applies by the same means to any other relevant proteins/peptides/enzymes, such as class II or III PI3K.

As used herein, the term "subject" refers to an animal. Typically the animal is a mammal. A subject also refers to for example, primates (*e.g.*, humans, male or female), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. In certain embodiments, the subject is a primate. In yet other embodiments, the subject is a human.

As used herein, the term "inhibit", "inhibition" or "inhibiting" refers to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

As used herein, the term "treat", "treating" or "treatment" of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment "treat", "treating" or "treatment" refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another embodiment, "treat", "treating" or "treatment" refers to modulating the disease or disorder, either physically, (*e.g.*, stabilization of a discernible symptom), physiologically, (*e.g.*, stabilization of a physical parameter), or both.

As used herein, the term "prevention" of any particular disease or disorder refers to the administration of a compound of the invention to a subject before any symptoms of that disease or disorder are apparent.

As used herein, a subject is "in need of" a treatment if such subject would benefit biologically, medically or in quality of life from such treatment.

As used herein, the term "a," "an," "the" and similar terms used in the context of the present invention (especially in the context of the claims) are to be construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context. The use of any and all examples, or exemplary language (*e.g.* "such as") provided herein is

intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed.

The term "compounds of the present invention" (unless specifically identified otherwise) refer to compounds of formula (I), compounds of the Examples, pharmaceutically acceptable salts of such compounds, and/or hydrates or solvates of such compounds, as well as, all stereoisomers (including diastereoisomers and enantiomers), tautomers and isotopically labeled compounds (including deuterium).

Compounds of the present invention are useful for treating diseases, conditions and disorders modulated by the inhibition of class I PI3Ks and the mTOR enzyme; consequently, the compounds of the present invention (including the compositions and processes used therein) may be used in the manufacture of a medicament for the therapeutic applications described herein. Hence, another embodiment of the present invention is a pharmaceutical composition comprising a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, diluent or carrier. In another embodiment of the present invention there is provided a pharmaceutical composition comprising a compound of the present invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, diluent or carrier.

A typical formulation is prepared by mixing a compound of the present invention and a carrier, diluent or excipient. Suitable carriers, diluents and excipients are well known to those skilled in the art and include materials such as carbohydrates, waxes, water soluble and/or swellable polymers, hydrophilic or hydrophobic materials, gelatin, oils, solvents, water, and the like. The particular carrier, diluent or excipient used will depend upon the means and purpose for which the compound of the present invention is being applied. Solvents are generally selected based on solvents recognized by persons skilled in the art as safe (GRAS) to be administered to a mammal. In general, safe solvents are non-toxic aqueous solvents such as water and other non-toxic solvents that are soluble or miscible in water. Suitable aqueous solvents include water, ethanol, propylene glycol, polyethylene glycols (e.g., PEG400, PEG300), etc. and mixtures thereof. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present

invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

The formulations may be prepared using conventional dissolution and mixing procedures. For example, the bulk drug substance (i.e., compound of the present invention or stabilized form of the compound (e.g., complex with a cyclodextrin derivative or other known complexation agent)) is dissolved in a suitable solvent in the presence of one or more of the excipients. The compound of the present invention is typically formulated into pharmaceutical dosage forms to provide an easily controllable dosage of the drug and to give the patient an elegant and easily handleable product.

The pharmaceutical composition (or formulation) for application may be packaged in a variety of ways depending upon the method used for administering the drug. Generally, an article for distribution includes a container having deposited therein the pharmaceutical formulation in an appropriate form. Suitable containers are well-known to those skilled in the art and include materials such as bottles (plastic and glass), sachets, ampoules, plastic bags, metal cylinders, and the like. The container may also include a tamper-proof assemblage to prevent indiscreet access to the contents of the package. In addition, the container has deposited thereon a label that describes the contents of the container. The label may also include appropriate warnings.

In one embodiment, the invention relates to the treatment of cellular proliferative diseases such as tumor and/or cancerous cell growth mediated by PI3K and/or mTOR. Diseases may include those showing overexpression or amplification of PI3K alpha, Rheb, somatic mutation of PIK3CA or germline mutations or somatic mutation of PTEN, TSC1, TSC2, or mutations and translocation of p85α that serve to up-regulate the p85-p110 complex. In particular, the compounds are useful in the treatment of human or animal (e.g., murine) cancers, including, for example, sarcoma; lung; bronchus; prostate; breast (including sporadic breast cancers and sufferers of Cowden disease); pancreas; gastrointestinal cancer; colon; rectum; colon carcinoma; colorectal adenoma; thyroid; liver; intrahepatic bile duct; hepatocellular; adrenal gland; stomach; gastric; glioma; glioblastoma; endometrial; melanoma; kidney; renal pelvis; urinary bladder; uterine corpus; uterine cervix; vagina; ovary; multiple myeloma; esophagus; a leukaemia; acute myelogenous leukemia; chronic myelogenous leukemia; lymphocytic leukemia; myeloid leukemia; brain; a carcinoma of the brain; oral cavity and pharynx; larynx; small intestine; non-Hodgkin lymphoma; melanoma; villous colon adenoma; a neoplasia; a neoplasia of epithelial character; lymphomas; a mammary carcinoma; basal cell carcinoma; squamous cell carcinoma; actinic keratosis;

tumor diseases, including solid tumors; a tumor of the neck or head; polycythemia vera; essential thrombocythemia; myelofibrosis with myeloid metaplasia; and Walden stroem disease.

In other embodiments, the condition or disorder (e.g. PI3K-mediated) is selected from the group consisting of: polycythemia vera, essential thrombocythemia, myelofibrosis with myeloid metaplasia, asthma, COPD, ARDS, Loffler's syndrome, eosinophilic pneumonia, parasitic (in particular metazoan) infestation (including tropical eosinophilia), bronchopulmonary aspergillosis, polyarteritis nodosa (including Churg-Strauss syndrome), eosinophilic granuloma, eosinophil-related disorders affecting the airways occasioned by drug-reaction, psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforme, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, pemphisus, epidermolysis bullosa acquisita, autoimmune haematogical disorders (e.g. haemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, scleroderma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (e.g. ulcerative colitis and Crohn's disease), endocrine opthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary biliary cirrhosis, uveitis (anterior and posterior), interstitial lung fibrosis, psoriatic arthritis, glomerulonephritis, cardiovascular diseases, atherosclerosis, hypertension, deep venous thrombosis, stroke, myocardial infarction, unstable angina, thromboembolism, pulmonary embolism, thrombolytic diseases, acute arterial ischemia, peripheral thrombotic occlusions, and coronary artery disease, reperfusion injuries, retinopathy, such as diabetic retinopathy or hyperbaric oxygen-induced retinopathy, and conditions characterized by elevated intraocular pressure or secretion of ocular aqueous humor, such as glaucoma.

Additional syndromes with an established or potential molecular link to dysregulation of mTOR kinase activity are, for instance, described in “K. Inoki et al. ; Disregulation of the TSC-mTOR pathway in human disease, Nature Genetics, vol 37, 19-24”; “D.M. Sabatini; mTOR and cancer: insights into a complex relationship, Nature Reviews, vol. 6, 729-734”; and in “B.T. Hennessy et al.; Exploiting the PI3K/Akt pathway for cancer drug discovery, Nature Reviews, vol. 4, 988-1004”, and are as follows:

- Organ or tissue transplant rejection, e.g. for the treatment of recipients of e.g. heart, lung, combined heart-lung, liver, kidney, pancreatic, skin or corneal transplants; graft-versus-host disease, such as following bone marrow transplantation;

- Restenosis
- Tuberous sclerosis
- Lymphangioleiomyomatosis
- Retinitis pigmentosis and other retinal degenerative disorders
- Autoimmune diseases including encephalomyelitis, insulin-dependent diabetes mellitus, lupus, dermatomyositis, arthritis and rheumatic diseases
- Steroid-resistant acute Lymphoblastic Leukaemia
- Fibrotic diseases including scleroderma, pulmonary fibrosis, renal fibrosis, cystic fibrosis
- Pulmonary hypertension
- Immunomodulation
- Multiple sclerosis
- VHL syndrome
- Carney complex
- Familial adenonamtous polyposis
- Juvenile polyposis syndrome
- Birt-Hogg-Duke syndrome
- Familial hypertrophic cardiomyopathy
- Wolf-Parkinson-White syndrome
- Neurodegenerative disorders such as Parkinson's Disease, Huntington's Disease, Alzheimer's Disease and dementias caused by tau mutations, spinocerebellar ataxia type 3, motor neuron disease caused by SOD1 mutations, neuronal ceroid lipofucinoses/Batten disease (pediatric neurodegeneration)
- wet and dry macular degeneration
- muscle wasting (atrophy, cachexia) and myopathies such as Danon's disease.
- bacterial and viral infections including M. tuberculosis, group A streptococcus, HSV type I, HIV infection
- Neurofibromatosis including Neurofibromatosis type 1, and
- Peutz-Jeghers syndrome, Cowden's disease.

Compounds with an inhibitory activity on mTORC1 have shown benefit in immunomodulation and in treating proliferative diseases such as advance renal cell carcinoma or Tubero-Sclerosis (TSC) germ line mutation associated disorders.

The catalytic inhibition of mTOR Ser/Thr kinase activity or class I PI3 kinases activity and in particular dual class I PI3-kinase(s) and mTOR kinase inhibition may be useful for the treatment of PI3K/Akt/mTOR pathway dependent diseases. The efficacy of a dual PI3

kinase / mTOR inhibitor in malignant glioma has been recently described (Cancer Cell 9, 341 – 349).

For the above uses the required dosage will of course vary depending on the mode of administration, the particular condition to be treated and the effect desired. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.03 to about 100.0 mg/kg per body weight, e.g. about 0.03 to about 10.0 mg/kg per body weight. An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5 mg to about 3 g, e.g. about 5 mg to about 1.5 g, conveniently administered, for example, in divided doses up to four times a day or in retard form. Suitable unit dosage forms for oral administration comprise from ca. 0.1 to about 500 mg, e.g. about 1.0 to about 500 mg active ingredient.

In general, compounds of the present invention will be administered as pharmaceutical compositions by any one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository), or parenteral (e.g., intramuscular, intravenous or subcutaneous) administration. The preferred manner of administration is oral using a convenient daily dosage regimen that can be adjusted according to the degree of affliction. Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate compositions. Another preferred manner for administering compounds of the present invention is inhalation. This is an effective method for delivering a therapeutic agent directly to the respiratory tract.

The compounds of the present invention may be administered in free form or in pharmaceutically acceptable salt form e.g. as indicated above. Such salts may be prepared in conventional manner and exhibit the same order of activity as the free compounds.

Consequently, the invention also provides:

- a method for preventing or treating conditions, disorders or diseases mediated by the activation of the PI3K (e.g. PI3 kinase alpha) and/or mTOR enzymes e.g. such as indicated above, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of the present invention or a pharmaceutically acceptable salt thereof. In one embodiment, there is provided a method for preventing or treating cancer or a neurodegenerative disorder, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of the present invention or a pharmaceutically acceptable salt thereof. In another embodiment, the

neurodegenerative disorder is Parkinson's, Huntington's or Alzheimer's Disease. In yet another embodiment, the neurodegenerative disorder is Huntington's Disease.

- a compound of the present invention, or a pharmaceutically acceptable salt thereof, for use as a medicament, e.g. in any of the methods as indicated herein.
- a compound of the present invention, or a pharmaceutically acceptable salt thereof, for use as pharmaceutical, e.g. in any of the methods as indicated herein, in particular for the use in one or more phosphatidylinositol 3-kinase mediated diseases. In one embodiment, there is provided a compound of the present invention, or a pharmaceutically acceptable salt thereof, for use in the treatment or prevention of cancer or a neurodegenerative disorder. In another embodiment, the neurodegenerative disorder is Parkinson's, Huntington's or Alzheimer's Disease. In yet another embodiment, the neurodegenerative disorder is Huntington's Disease.
- the use of a compound of the present invention, or a pharmaceutically acceptable salt thereof, in any of the methods as indicated herein, in particular for the treatment or prevention of one or more phosphatidylinositol 3-kinase mediated diseases. In one embodiment, there is provided the use of a compound of the present invention, or a pharmaceutically acceptable salt thereof, for the treatment or prevention of cancer or a neurodegenerative disorder. In another embodiment, the neurodegenerative disorder is Parkinson's, Huntington's or Alzheimer's Disease. In yet another embodiment, the neurodegenerative disorder is Huntington's Disease.
- the use of a compound of the present invention, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of one or more phosphatidylinositol 3-kinase mediated diseases. In one embodiment, there is provided the use of a compound of the present invention, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of cancer or a neurodegenerative disorder. In another embodiment, the neurodegenerative disorder is Parkinson's, Huntington's or Alzheimer's Disease. In yet another embodiment, the neurodegenerative disorder is Huntington's Disease.

PI3K serves as a second messenger node that integrates parallel signaling pathways, evidence is emerging that the combination of a PI3K inhibitor with inhibitors of other pathways will be useful in treating cancer and proliferative diseases in humans. Approximately 20-30% of human breast cancers overexpress Her-2/neu-ErbB2, the target for the drug trastuzumab. Although trastuzumab has demonstrated durable responses in some patients expressing Her2/neu-ErbB2, only a subset of these patients respond. Further studies have indicated that this limited response rate can be substantially improved by the combination of trastuzumab with inhibitors of PI3K or the PI3K/AKT pathway (Chan et al.,

Breast Can. Res. Treat. 91:187 (2005), Woods Ignatoski et al., Brit. J. Cancer 82:666 (2000), Nagata et al., Cancer Cell 6:117 (2004)).

A variety of human malignancies express activitating mutations or increased levels of Her1/EGFR and a number of antibody and small molecule inhibitors have been developed against this receptor tyrosine kinase including tarceva, gefitinib and erbitux. However, while EGFR inhibitors demonstrate anti-tumor activity in certain human tumors (e.g., NSCLC), they fail to increase overall patient survival in all patients with EGFR-expressing tumors. This may be rationalized by the fact that many downstream targets of Her1/EGFR are mutated or deregulated at high frequencies in a variety of malignancies, including the PI3K/Akt pathway. For example, gefitinib inhibits the growth of an adenocarcinoma cell line in in vitro assays. Nonetheless, sub-clones of these cell lines can be selected that are resistant to gefitinib that demonstrate increased activation of the PI3/Akt pathway. Down-regulation or inhibition of this pathway renders the resistant sub-clones sensitive to gefitinib (Kokubo et al., Brit. J. Cancer 92:1711 (2005)). Furthermore, in an in vitro model of breast cancer with a cell line that harbors a PTEN mutation and over-expresses EGFR inhibition of both the PI3K/Akt pathway and EGFR produced a synergistic effect (She et al., Cancer Cell 8:287-297(2005)). These results indicate that the combination of gefitinib and PI3K/Akt pathway inhibitors would be an attractive therapeutic strategy in cancer.

The combination of AEE778 (an inhibitor of Her-2/neu/ErbB2, VEGFR and EGFR) and RAD001 (an inhibitor of mTOR, a downstream target of Akt) produced greater combined efficacy that either agent alone in a glioblastoma xenograft model (Goudar et al., Mol. Cancer. Ther. 4:101-112 (2005)).

Anti-estrogens, such as tamoxifen, inhibit breast cancer growth through induction of cell cycle arrest that requires the action of the cell cycle inhibitor p27Kip. Recently, it has been shown that activation of the Ras-Raf-MAP Kinase pathway alters the phosphorylation status of p27Kip such that its inhibitory activity in arresting the cell cycle is attenuated, thereby contributing to anti-estrogen resistance (Donovan, et al, J. Biol. Chem. 276:40888, (2001)). As reported by Donovan et al., inhibition of MAPK signaling through treatment with MEK inhibitor reversed the aberrant phosphorylation status of p27 in hormone refractory breast cancer cell lines and in so doing restored hormone sensitivity. Similarly, phosphorylation of p27Kip by Akt also abrogates its role to arrest the cell cycle (Viglietto et al., Nat Med. 8:1145 (2002)).

Accordingly, in a further aspect, the compounds of formula I may be useful in the treatment of hormone dependent cancers, such as breast and prostate cancers. By this use, it is aimed to reverse hormone resistance commonly seen in these cancers with conventional anticancer agents.

In hematological cancers, such as chronic myelogenous leukemia (CML), chromosomal translocation is responsible for the constitutively activated BCR-Abl tyrosine kinase. The afflicted patients are responsive to imatinib, a small molecule tyrosine kinase inhibitor, as a result of inhibition of Abl kinase activity. However, many patients with advanced stage disease respond to imatinib initially, but then relapse later due to resistance-conferring mutations in the Abl kinase domain. In vitro studies have demonstrated that BCR-Ab1 employs the Ras-Raf kinase pathway to elicit its effects. In addition, inhibiting more than one kinase in the same pathway provides additional protection against resistance-conferring mutations.

Accordingly, in another aspect, the compounds of the present invention are used in combination with at least one additional agent selected from the group of kinase inhibitors, such as Gleevec®, in the treatment of hematological cancers, such as chronic myelogenous leukemia (CML). By this use, it is aimed to reverse or prevent resistance to said at least one additional agent.

Because activation of the PI3K/Akt pathway drives cell survival, inhibition of the pathway in combination with therapies that drive apoptosis in cancer cells, including radiotherapy and chemotherapy, will result in improved responses (Ghobrial et al., CA Cancer J. Clin 55:178-194 (2005)). As an example, combination of PI3 kinase inhibitor with carboplatin demonstrated synergistic effects in both in vitro proliferation and apoptosis assays as well as in in vivo tumor efficacy in a xenograft model of ovarian cancer (Westfall and Skinner, Mol. Cancer Ther. 4:1764-1771 (2005)).

In addition to cancer and proliferative diseases, there is accumulating evidence that inhibitors of Class 1A and 1B PI3 kinases would be therapeutically useful in others disease areas. The inhibition of p110β, the PI3K isoform product of the PIK3CB gene, has been shown to be involved in shear-induced platelet activation (Jackson et al., Nature Medicine 11:507-514 (2005)). Thus, a PI3K inhibitor that inhibits p110β would be useful as a single agent or in combination in anti-thrombotic therapy. The isoform p110δ, the product of the PIK3CD gene, is important in B cell function and differentiation (Clayton et al., J. Exp. Med. 196:753-763 (2002)), T-cell dependent and independent antigen responses (Jou et al., Mol. Cell. Biol.

22:8580-8590 (2002)) and mast cell differentiation (Ali et al., Nature 431:1007-1011 (2004)). Thus, it is expected that p110δ-inhibitors would be useful in the treatment of B-cell driven autoimmune diseases and asthma. Finally, the inhibition of p110γ, the isoform product of the PI3KCG gene, results in reduced T, but not B cell, response (Reif et al., J. Immunol. 173:2236-2240 (2004)) and its inhibition demonstrates efficacy in animal models of autoimmune diseases (Camps et al., Nature Medicine 11:936-943 (2005), Barber et al., Nature Medicine 11:933-935 (2005)).

The invention further provides pharmaceutical compositions comprising at least one compound of the present invention, together with a pharmaceutically acceptable excepient suitable for administration to a human or animal subject, either alone or together with other anticancer agents.

The invention further provides methods of treating human or animal subjects suffering from a cellular proliferative disease, such as cancer. The invention thus provides methods of treating a human or animal subject in need of such treatment, comprising administering to the subject a therapeutically effective amount of a compound of the present invention either alone or in combination with one or more other anticancer agents. In particular, compositions will either be formulated together as a combination therapeutic or administered separately. Suitable anticancer agents for use with a compound of the present invention include, but are not limited to, one or more compounds selected from the group consisting of kinase inhibitors, anti-estrogens, anti androgens, other inhibitors, cancer chemotherapeutic drugs, alkylating agents, chelating agents , biological response modifiers, cancer vaccines, agents for antisense therapy as set forth below:

A. Kinase Inhibitors: Kinase inhibitors for use as anticancer agents in conjunction with the compound of the present invention include inhibitors of Epidermal Growth Factor Receptor (EGFR) kinases such as small molecule quinazolines, for example gefitinib (US 5457105, US 5616582, and US 5770599), ZD-6474 (WO 01/32651), erlotinib (Tarceva®, US 5,747,498 and WO 96/30347), and lapatinib (US 6,727,256 and WO 02/02552); Vascular Endothelial Growth Factor Receptor (VEGFR) kinase inhibitors, including SU-11248 (WO 01/60814), SU 5416 (US 5,883,113 and WO 99/61422), SU 6668 (US 5,883,113 and WO 99/61422), CHIR-258 (US 6,605,617 and US 6,774,237), vatalanib or PTK-787 (US 6,258,812), VEGF-Trap (WO 02/57423), B43-Genistein (WO-09606116), fenretinide (retinoic acid p-hydroxyphenylamine) (US 4,323,581), IM-862 (WO 02/62826), bevacizumab or Avastin® (WO 94/10202), KRN-951, 3-[5-(methylsulfonylpiperadine methyl)-indolyl]-quinolone, AG-13736 and AG-13925, pyrrolo[2,1-f][1,2,4]triazines, ZK-304709, Veglin®, VMDA-3601, EG-004, CEP-701 (US 5,621,100), Cand5 (WO 04/09769); Erb2 tyrosine kinase inhibitors such

as pertuzumab (WO 01/00245), trastuzumab, and rituximab; Akt protein kinase inhibitors, such as RX-0201; Protein Kinase C (PKC) inhibitors, such as LY-317615 (WO 95/17182), and perifosine (US 2003171303); Raf/Map/MEK/Ras kinase inhibitors including sorafenib (BAY 43-9006), ARQ-350RP, LErafAON, BMS-354825 AMG-548, and others disclosed in WO 03/82272; Fibroblast Growth Factor Receptor (FGFR) kinase inhibitors; Cell Dependent Kinase (CDK) inhibitors, including CYC-202 or roscovitine (WO 97/20842 and WO 99/02162); Platelet-Derived Growth Factor Receptor (PDGFR) kinase inhibitors such as CHIR-258, 3G3 mAb, AG-13736, SU-11248 and SU6668; and Bcr-Abl kinase inhibitors and fusion proteins such as STI-571 or Gleevec® (imatinib).

B. Anti-Estrogens: Estrogen-targeting agents for use in anticancer therapy in conjunction with the compound of the present invention include Selective Estrogen Receptor Modulators (SERMs) including tamoxifen, toremifene, raloxifene; aromatase inhibitors including Arimidex® or anastrozole; Estrogen Receptor Downregulators (ERDs) including Faslodex® or fulvestrant.

C. Anti-Androgens: Androgen-targeting agents for use in anticancer therapy in conjunction with the compound of the present invention include flutamide, bicalutamide, finasteride, aminoglutethamide, ketoconazole, and corticosteroids.

D. Other Inhibitors: Other inhibitors for use as anticancer agents in conjunction with the compound of the present invention include protein farnesyl transferase inhibitors including tipifarnib or R-115777 (US 2003134846 and WO 97/21701), BMS-214662, AZD-3409, and FTI-277; topoisomerase inhibitors including merbarone and diflomotecan (BN-80915); mitotic kinesin spindle protein (KSP) inhibitors including SB-743921 and MKI-833; proteasome modulators such as bortezomib or Velcade® (US 5,780,454), XL-784; and cyclooxygenase 2 (COX-2) inhibitors including non-steroidal antiinflammatory drugs I (NSAIDs).

E. Cancer Chemotherapeutic Drugs: Particular cancer chemotherapeutic agents for use as anticancer agents in conjunction with the compound of the present invention include anastrozole (Arimidex®), bicalutamide (Casodex®), bleomycin sulfate (Blenoxane®), busulfan (Myleran®), busulfan injection (Busulfex®), capecitabine (Xeloda®), N4-pentoxycarbonyl-5-deoxy-5-fluorocytidine, carboplatin (Paraplatin®), carmustine (BiCNU®), chlorambucil (Leukeran®), cisplatin (Platinol®), cladribine (Leustatin®), cyclophosphamide (Cytoxan® or Neosar®), cytarabine, cytosine arabinoside (Cytosar-U®), cytarabine liposome injection (DepoCyt®), dacarbazine (DTIC-Dome®), dactinomycin (Actinomycin D, Cosmegan), daunorubicin hydrochloride (Cerubidine®), daunorubicin citrate liposome injection (DaunoXome®), dexamethasone, docetaxel (Taxotere®), doxorubicin hydrochloride (Adriamycin®, Rubex®), etoposide (Vepesid®), fludarabine phosphate (Fludara®), 5-fluorouracil (Adrucil®, Efudex®), flutamide (Eulexin®), tezacitibine, Gemcitabine (difluorodeoxycitidine), hydroxyurea (Hydrea®), Idarubicin (Idamycin®), ifosfamide (IFEX®),

irinotecan (Camptosar®), L-asparaginase (ELSPAR®), leucovorin calcium, melphalan (Alkeran®), 6-mercaptopurine (Purinethol®), methotrexate (Folex®), mitoxantrone (Novantrone®), mylotarg, paclitaxel (Taxol®), phoenix (Yttrium90/MX-DTPA), pentostatin, polifeprosan 20 with carmustine implant (Gliadel®), tamoxifen citrate (Nolvadex®), teniposide (Vumon®), 6-thioguanine, thiotepa, tirapazamine (Tirazone®), topotecan hydrochloride for injection (Hycamptin®), vinblastine (Velban®), vincristine (Oncovin®), and vinorelbine (Navelbine®).

F. Alkylating Agents: Alkylating agents for use in conjunction with the compound of the present invention include VNP-40101M or cloretizine, oxaliplatin (US 4,169,846, WO 03/24978 and WO 03/04505), glufosfamide, mafosfamide, etopophos (US 5,041,424), prednimustine; treosulfan; busulfan; irofluven (acylfulvene); penclomedine; pyrazoloacridine (PD-115934); O6-benzylguanine; decitabine (5-aza-2-deoxycytidine); brostallicin; mitomycin C (MitoExtra); TLK-286 (Telcyta®); temozolomide; trabectedin (US 5,478,932); AP-5280 (Platinate formulation of Cisplatin); porfiromycin; and clearazide (meclorethamine).

G. Chelating Agents: Chelating agents for use in conjunction with the compound of the present invention include tetrathiomolybdate (WO 01/60814); RP-697; Chimeric T84.66 (cT84.66); gadofosveset (Vasovist®); deferoxamine; and bleomycin optionally in combination with electorporation (EPT).

H. Biological Response Modifiers: Biological response modifiers, such as immune modulators, for use in conjunction with the compound of the present invention include staurosprine and macrocyclic analogs thereof, including UCN-01, CEP-701 and midostaurin (see WO 02/30941, WO 97/07081, WO 89/07105, US 5,621,100, WO 93/07153, WO 01/04125, WO 02/30941, WO 93/08809, WO 94/06799, WO 00/27422, WO 96/13506 and WO 88/07045); squalamine (WO 01/79255); DA-9601 (WO 98/04541 and US 6,025,387); alemtuzumab; interferons (e.g. IFN-a, IFN-b etc.); interleukins, specifically IL-2 or aldesleukin as well as IL-1, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, and active biological variants thereof having amino acid sequences greater than 70% of the native human sequence; altretamine (Hexalen®); SU 101 or leflunomide (WO 04/06834 and US 6,331,555); imidazoquinolines such as resiquimod and imiquimod (US 4,689,338, 5,389,640, 5,268,376, 4,929,624, 5,266,575, 5,352,784, 5,494,916, 5,482,936, 5,346,905, 5,395,937, 5,238,944, and 5,525,612); and SMIPs, including benzazoles, anthraquinones, thiosemicarbazones, and tryptanthrins (WO 04/87153, WO 04/64759, and WO 04/60308).

I. Cancer Vaccines: Anticancer vaccines for use in conjunction with the compound of the present invention include Avicine® (Tetrahedron Lett. 26:2269-70 (1974)); oregovomab (OvaRex®); Theratope® (STn-KLH); Melanoma Vaccines; GI-4000 series (GI-4014, GI-4015, and GI-4016), which are directed to five mutations in the Ras protein; GlioVax-1; MelaVax; Advexin® or INGN-201 (WO 95/12660); Sig/E7/LAMP-1, encoding HPV-16 E7;

MAGE-3 Vaccine or M3TK (WO 94/05304); HER-2VAX; ACTIVE, which stimulates T-cells specific for tumors; GM-CSF cancer vaccine; and Listeria monocytogenes-based vaccines.

J. Antisense Therapy: Anticancer agents for use in conjunction with the compound of the present invention also include antisense compositions, such as AEG-35156 (GEM-640); AP-12009 and AP-11014 (TGF-beta2-specific antisense oligonucleotides); AVI-4126; AVI-4557; AVI-4472; oblimersen (Genasense®); JFS2; aprinocarsen (WO 97/29780); GTI-2040 (R2 ribonucleotide reductase mRNA antisense oligo) (WO 98/05769); GTI-2501 (WO 98/05769); liposome-encapsulated c-Raf antisense oligodeoxynucleotides (LErafAON) (WO 98/43095); and Sirna-027 (RNAi-based therapeutic targeting VEGFR-1 mRNA).

The compound of the present invention may also be combined in a pharmaceutical composition with bronchiodilatory or antihistamine drugs substances. Such bronchiodilatory drugs include anticholinergic or antimuscarinic agents, in particular ipratropium bromide, oxitropium bromide, and tiotropium bromide, and β-2- adrenoreceptor agonists such as salbutamol, terbutaline, salmeterol, carmoterol, milveterol and, especially, formoterol or indacaterol. Co-therapeutic antihistamine drug substances include cetirizine hydrochloride, clemastine fumarate, promethazine, loratadine, desloratadine diphenhydramine and fexofenadine hydrochloride.

The invention provides in a further aspect a combination comprising a compound of the present invention and one or more compounds that are useful for the treatment of a thrombolytic disease, heart disease, stroke, etc. Such compounds include aspirin, a streptokinase, a tissue plasminogen activator, a urokinase, a anticoagulant, antiplatelet drugs (e.g, PLAVIX; clopidogrel bisulfate), a statin (e.g., LIPITOR or Atorvastatin calcium), ZOCOR (Simvastatin), CRESTOR (Rosuvastatin), etc.), a Beta blocker (e.g., Atenolol), NORVASC (amlodipine besylate), and an ACE inhibitor (e.g., lisinopril).

The invention provides in a further aspect a combination comprising a compound of the present invention and one or more compounds that are useful for the treatment of antihypertension. Such compounds include ACE inhibitors, lipid lowering agents such as statins, LIPITOR (Atorvastatin calcium), calcium channel blockers such as NORVASC (amlodipine besylate).

The invention provides in a further aspect a combination comprising a compound of the present invention and one or more compounds selected from the group consisting of fibrates, beta-blockers, NEPI inhibitors, Angiotensin-2 receptor antagonists and platelet aggregation inhibitors.

The invention provides in a further aspect a combination comprising a compound of the present invention and a compound suitable for the treatment of inflammatory diseases, including rheumatoid arthritis. Such compound may be selected from the group consisting of TNF-α inhibitors such as anti-TNF-α monoclonal antibodies (such as REMICADE, CDP-870) and D2E7 (HUMIRA) and TNF receptor immunoglobulin fusion molecules (such as ENBREL), IL-1 inhibitors, receptor antagonists or soluble IL-1Rα(e.g. KINERET or ICE inhibitors), nonsterodial anti-inflammatory agents (NSAIDS), piroxicam, diclofenac, naproxen, flurbiprofen, fenoprofen, ketoprofen ibuprofen, fenamates, mefenamic acid, indomethacin, sulindac, apazone, pyrazolones, phenylbutazone, aspirin, COX-2 inhibitors (such as CELEBREX (celecoxib), PREXIGE (lumiracoxib)), metalloprotease inhibitors (preferably MMP-13 selective inhibitors), p2x7 inhibitors, α2αinhibitors, NEUROTIN, pregabalin, low dose methotrexate, leflunomide, hydroxyxchloroquine, d-penicillamine, auranofin or parenteral or oral gold.

The invention provides in a further aspect a combination comprising a compound of the present invention and a compound suitable for the treatment of osteoarthritis. Such compound may be selected from the group consisting of standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) such as piroxicam, diclofenac, propionic acids such as naproxen, flurbiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, COX-2 inhibitors such as celecoxib, valdecoxib, lumiracoxib and etoricoxib, analgesics and intraarticular therapies such as corticosteroids and hyaluronic acids such as hyalgan and synvisc.

The invention provides in a further aspect a combination comprising a compound of the present invention and an antiviral agent and/or an antisepsis compound. Such antiviral agent may be selected from the group consisting of Viracept, AZT, acyclovir and famciclovir. Such antisepsis compound may be selected from the group consisting of Valant.

The invention provides in a further aspect a combination comprising a compound of the present invention and one or more agents selected from the group consisting of CNS agents such as antidepressants (sertraline), anti-Parkinsonian drugs (such as deprenyl, L-dopa, Requip, Mirapex; MAOB inhibitors (such as selegine and rasagiline); comP inhibitors (such as Tasmar); A-2 inhibitors; dopamine reuptake inhibitors; NMDA antagonists; Nicotine agonists; Dopamine agonists; and inhibitors of neuronal nitric oxide synthase).

The invention provides in a further aspect a combination comprising a compound of the present invention and one or more anti-Alzheimer's drugs. Such anti-Alzheimer Drug may be selected from the group consisting of donepezil, tacrine, $\alpha 2\delta$inhibitors, NEUROTIN, pregabalin, COX-2 inhibitors, propentofylline or metryfonate.

The invention provides in a further aspect a combination comprising a compound of the present invention and anosteoporosis agents and/or an immunosuppressant agent. Such osteoporosis agents may be selected from the group consisting of EVISTA (raloxifene hydrochloride), droloxifene, lasofoxifene or fosomax. Such immunosuppressant agents may be selected from the group consisting of FK-506 and rapamycin.

In another aspect of the preferred embodiments, kits that include one or more compound of the present invention and a combination partner as disclosed herein are provided. Representative kits include a PI3K inhibitor compound (e.g., a compound of the present invention) and a package insert or other labeling including directions for treating a cellular proliferative disease by administering a PI3K inhibitory amount of the compound(s).

Combined pharmaceutical compositions comprising a compound of the present invention in free form or in pharmaceutically acceptable salt form and further comprising a combination partner (either in one dosage unit form or as a kit of parts) in association with at least one pharmaceutical acceptable carrier and/or diluent may be manufactured in conventional manner by mixing with a pharmaceutically acceptable carrier and/or diluent with said active ingredients.

Consequently, the invention provides in further aspects

- a combination, e.g. for use in any of the methods described herein, comprising a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof, and another therapeutic agent, for simultaneous or sequential administration.
- a product comprising a compound of the present invention, or a pharmaceutically acceptable salt thereof, and another therapeutic agent.
- a product comprising a compound of the present invention, or a pharmaceutically acceptable salt thereof, and another therapeutic agent as a combined preparation for use in therapy, e.g. for use in any of the therapies described herein. In one embodiment, the therapy is the treatment or prevention of cancer or a neurodegenerative disorder. In another embodiment, the therapy is the treatment or

prevention of Parkinson's, Huntington's or Alzheimer's Disease. In yet another embodiment, the therapy is the treatment or prevention of Huntington's Disease.

- a combined pharmaceutical composition comprising a compound of the present invention, or a pharmaceutically acceptable salt thereof, and another therapeutic agent.
- a combined pharmaceutical composition comprising a compound of the present invention, or a pharmaceutically acceptable salt thereof, another therapeutic agent and optionally one or more pharmaceutically acceptable carrier material(s) and/or diluents. Such combined pharmaceutical composition may be in the form of one dosage unit form or as a kit of parts.
- a method as defined above comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof, and another therapeutic agent, e.g. as indicated above.
- a pharmaceutical combination, e.g. a kit, comprising a) a first agent which is a compound of the present invention as disclosed herein, or a pharmaceutically acceptable salt thereof, and b) another therapeutic agent, e.g. as indicated above; whereby such kit may comprise instructions for its administration.

The following examples of compounds of the present invention illustrate the invention without limiting the scope thereof. Methods for preparing such compounds are described hereinafter.

EXAMPLES

Abbreviations

Ac/ac/Oac	acetyl CH3CO-
AcOEt/EA/EtOAc	ethyl acetate
AcOH	acetic acid
ACN/MeCN/CH_3CN	acetonitrile
Biotage	flash Chromatography
brs	broad singlet
$CDCl_3$	deuterated chloroform
CsF	cesium fluoride
Cu(OAc)	copper(I) acetate
d	doublet
Da	dalton
DAD-UV	ultra violet diode array detection/ ultra violet diode array detector

DCM/CH_2Cl_2	dichloromethane
deg	degree
dt	doublet triplet
DIPEA	di-isopropylethyl amine
DMA	dimethylacetamide
DMF	dimethylformide
DMSO	dimethylsulfoxide
DMSO-d_6	deuterated dimethylsulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
e.g.	for example
equiv	equivalent
Et_2O	ethyl ether
EtOH	ethanol
Gilston/Prep-LC /Preparative HPLC	HPLC - (high performance) liquid chromatography
HPLC/LC	high performance liquid chromatography/liquid chromatography
hr/hrs	hours
i-PrOH	iso-propanol
KOAc	potassium acetate
L	liter
LC	liquid chromatography
LC-MS	liquid chromatography-mass spectrometry
LC-UV	liquid chromatography-with Ultra Violet detection
MeOH	methanol
CD_3OD	deuterated methanol
m	multitet
MS	mass spectrometry
NMP	N-Methyl-2-pyrrolidone/methylpyrrolidone
NMR	nuclear magnetic resonance
^{1}HNMR	proton nuclear magnetic resonance
$Pd(OAc)_2$	palladium(II) acetate
$PdCl_2(PPh_3)_2$	bis(triphenylphosphine) palladium(II) chloride
$PdCl_2$(dppf)	1,1'-Bis(diphenylphosphino)ferrocene palladium (II) chloride
PPh_3	triphenyl phosphine
RT/rt	room temperature
s	singlet
t	triplet

TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
UV	ultraviolet
uW/MW	microwave heating source
wt%	weight percent

ANALYTICAL METHODS

NMR: proton spectra are recorded on a Bruker 400 MHz ultrashield spectrometer unless otherwise noted. Chemical shifts are reported in ppm relative to methanol (δ 3.31), dimethyl sulfoxide (δ 2.50), or chloroform (δ 7.26). A small amount of the dry sample (2-5 mg) is dissolved in an appropriate deuterated solvent (1 mL). The shimming is automated and the spectra is obtained with 64 or more scans.

LC/MS:

The sample is dissolved in suitable solvent such as MeCN, DMSO or MeOH and is injected directly into the column using the automated sample handler. The analysis is done using with one of the following methods:

Method 1: compounds are analyzed on an Inertsil ODS-3 column (C18, 50 x 4.6 mm, 3 µm) with a 2 min gradient elution (20-80% acetonitrile/H_2O/5 mM ammonium formate) and a flow rate of 4 mL/min.

Method 2: GENERAL LC/MS method with acid mobile phase (0.1% formic acid) and fast gradient. Electrospray mass spectra (+) and (-), DAD-UV chromatogram 200-400 nm, scan range 120-1500 Da. Gradient: 20-80% MeCN/H_2O in 2 min (2 mL/min), 2µL injection. Column: Inertsil ODS3 C-18, 3 cm x 33 mm x 3.0 µm, 40 deg C.

Method 3: GENERAL LC/MS method with neutral mobile phase (5 mM $NH_4^+HCOO^-$) and fast (20-80%) gradient. Electrospray mass spectra (+) and (-), DAD-UV chromatogram 200-400 nm, scan range 120-1500 Da. Gradient: 20-80% MeCN/H_2O in 2 min (2 mL/min), 2µL injection. Column: Inertsil ODS3 C-18, 3 cm x 33 mm x 3.0 µm, 40 deg C.

Method 4: LC/MS method for NON-POLAR (greasy) compounds with acid mobile phase (0.1% formic acid) and fast (40-90%) gradient. Electrospray mass spectra (+) and (-), DAD-UV chromatogram 200-400 nm, scan range 120-1500 Da. Gradient: 40-90% MeCN/H_2O in 2 min (2 mL/min), 2µL injection. Column: Inertsil C8-3, 3 cm x 33 mm x 3.0 µm, 40 deg C.

Method 5: LC/MS method for NON-POLAR (greasy) compounds with neutral mobile phase (5mM $NH_4^+HCOO^-$) and fast (40-90%) gradient. Electrospray mass spectra (+) and (-), DAD-UV chromatogram 200-400nm, scan range 120-1500 Da. Gradient: 40-90% MeCN/H_2O in 2 min (2 mL/min), 2µL injection. Column: Inertsil C8-3, 3.0 cm x 33 mm x 3.0 µm, 40 deg C.

Method 6: LC/MS method with broad range (5-95%) gradient with acid mobile phase (0.1% Formic Acid). Electrospray mass spectra (+) and (-), DAD-UV chromatogram 200-400 nm, scan range 120-1500 Da. Gradient: 5-95% MeCN/H_2O in 2 min (2 mL/min), 2µL injection. Column: Inertsil C8-3, 3.0 cm x 33 mm x 3.0 µm, 40 deg C.

Method 7: LC/MS method with broad range (5-95%) gradient with neutral mobile phase (5 mM $NH_4^+HCOO^-$). Electrospray mass spectra (+) and (-), DAD-UV chromatogram 200-400 nm, scan range 120-1500 Da. Gradient: 5-95% MeCN/H_2O in 2 min (2 mL/min), 2µL injection. Column: Inertsil C8-3, 3 cm x 33 mm x 3.0 µm, 40 deg C.

Method 8: LC/MS method for POLAR compounds with acid mobile phase (0.1% formic acid) and slow (0-100%) gradient. Electrospray mass spectra (+) and (-), DAD-UV chromatogram 200-400 nm, scan range 120-1500 Da. Gradient: 0-100% MeCN/H_2O in 2 min (2 mL/min), 2µL injection. Column: Inertsil ODS3 (C-18, 3 cm x 33 mm x 3.0 µm, 40 degree C.)

Method 9: LC/MS method for POLAR compounds with neutral mobile phase (5mM $NH_4^+HCOO^-$) and slow (0-100%) gradient. Electrospray mass spectra (+) and (-), DAD-UV chromatogram 200-400 nm, scan range 120-1500 Da. Gradient: 0-100% MeCN/H_2O in 2 min (2 mL/min), 2µL injection. Column: Inertsil ODS-3 (C-18, 3 cm x 33 mm x 3.0 µm, 40 deg C.

Method 10: Compounds are analyzed on an Inertsil ODS-3 column (C8, 30mm x 3.0 mm, 3.0 *u*m) with a 2 min gradient elution (5-90% acetonitrile/H_2O/5 mM ammonium formate) and a flow rate of 2 mL/min.

Method 11: Compounds are analyzed on an Inertsil ODS-3 column (C8, 30mm x 3.0 mm, 3.0 *u*m) with a 2 min gradient elution (5-90% acetonitrile/H_2O/0.1% formic acid) and a flow rate of 2 mL/min.

HPLC purification utilizes a C8 or C18 column (30 x 100mm, 5 *u*m, brand: Sunfire or XTerra). The sample is dissolved in suitable solvent such as MeCN, DMSO or MeOH (maximum 5 mL) and is injected directly into the column using the automated sample handler. The purification is performed with an appropriate gradient using two methods (unless otherwise noted). **Method 1** consists of 0.1% TFA in 5%-95% ACN in H_2O. **Method 2** consists of 10 mM NH_4OHin 5%-95% ACN in H_2O.

Synthesis of boronic ester intermediates

The boronic ester intermediates used in the preparation of compounds of the present invention are either commercially available or may be prepared as described in the literature, or in an analogous manner, or can be prepared as described hereafter, or in an analogous manner.

Boronic ester 1: 4-(4,4,5,5-Tetramethyl-[1,3,2]dioxa borolan-2-yl)-1H-pyrrolo[2,3-b]pyridine

To a solution of 4-Bromo-7-azaindole (0.48 g, 2.41 mmol) in dioxane (12 mL) was added bis(pinacolato)diboron followed by bis(diphenylphosphino)ferrocene (0.067 g, 0.12 mmol). The mixture was degassed for 20 minutes using nitrogen, followed by addition of $PdCl_2$(dppf) catalyst (0.088 g, 0.12 mmol). Suspension was degassed for additional 5 minutes. Vial was seal and placed in an oil bath. The reaction was heated to 120 ^oC for 16 hours. After completion, the reaction mixture was allowed to cool to ambient temperature, suspension was filtered and solvent was removed under reduced pressure. The crude was directly purified on Biotage using 0-100 % gradient of EtOAC/Heptane. Further purification was done using preparartive HPLC (gradient 5%-95% with 3% n-propanol/acetonitrile over 3% n-propanol/water) to afford as a white solid (0.054 g, 9.2 %) LC/MS analysis using method 7, mass (ES+) m/z 245.4 ^1H NMR ($CDCl_3$) δ 9.03 (1H, brs), 8.24 (1H, d), 7.42 (1H, d), 7.30 (1H, d), 6.86 (1H,d), 1.31 (12H,s)

Boronic ester 2: [2-Methoxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-metha-nol

Boronic ester was synthesized using general procedure described in Scheme 3. The compound was isolated in 77 % yield as yellow oil. ^1H NMR (CD_3OD): δ 7.76 (1H, s), 7.67 (1H, d), 6.90 (1H, d), 4.62 (2H, s), 3.83 (3H, s), 1.32 (12H, s)

Boronic ester 3: [3-Methoxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-metha-nol

Boronic ester was synthesized using general procedure described in Scheme 3. The compound was isolated in 27 % yield as brown solid. ^1HNMR (DMSO-d_6): δ 7.24 (1H, s), 7.01 (1H, s), 6.99 (1H, s), 5.18 (1H, m), 4.47 (2H, d), 3.75 (3H, s), 1.29 (12H, s).

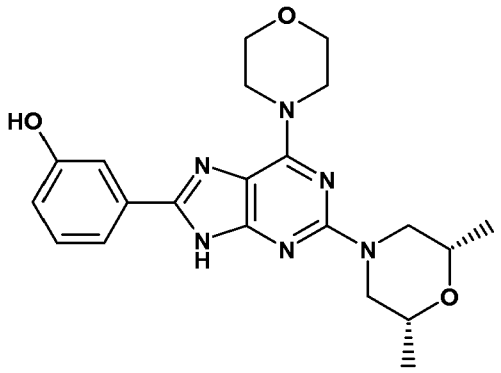
Boronic ester 4: BOC-3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzylamine

To a solution of 3-bromobenzylamine (0.79 g, 4.24 mmol), di-tertbutyldicarbonate (1.82 g, 8.5 mmol, 2.0 equiv) in 10 mL of CH_2Cl_2 was added triethylamine (1.29 g, 12.7 mmol, 3.0 equiv.)

After 2 hours of stirring the reaction was stopped and the solution was washed with water. Aqueous layer was extracted with CH_2Cl_2. Organic layers combined and dried over $MgSO_4$. Upon removal of solvent under reduced pressure, the crude was purified using flash column chromatography (Biotage, 0-60 % gradient of EtOAc/Heptane). The desired boronic ester was then synthesized using general coupling procedure described in Scheme 3. The compound was isolated in 59% yield as brown solid. ^{1}HNMR ($CDCl_3$): δ 7.61-7.62 (2H, m), 7.27-7.31 (1H, m), 7.24 (1H, t), 4.85 (1H,brs), 4.72 (2 H, brs), 1.37 (9H,s), 1.25 (12 H, s)

Example 1

Synthesis of 3-[2-((2S,6R)-2,6-Dimethyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purin-8-yl]-phenol



a) 2-Chloro-6-morpholin-4-yl-9H-purine

To a solution of 2,6-dichloro-9H-purine (1.2 g, 6.35 mmol) in *N*,*N*-dimethylformamide (5 mL) was added morpholine (553 mg, 6.35 mmol) followed by diisopropylethyl amine (1.2 mL, 6.87 mmol), dropwise via a syringe. The solution was stirred at room temperature for 1 hour until precipitate formed. The reaction mixture was then poured into water and the precipitate was filtered. Upon drying under high vacuum, 2-chloro-6-morpholin-4-yl-9H-purine was isolated as an off-white solid. (1.5 g, 99%) LC/MS analysis method 7, mass (ES+) m/z 240.2 ^{1}H NMR (DMSO-d_6): 13.21 (1H, brs), 8.15 (1H, s), 4.18 (4H, brs), 3.72 (4H, t)

b) 2-((2*S*,6*R*)-2,6-Dimethyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purine

To the solution of 2-chloro-6-morpholin-4-yl-9H-purine (1.5 g, 6.26 mmol) in DMA (5 mL) was added cis-2,6 dimethylmorpholine (1.42 g, 12.52 mmol), followed by DIPEA (2.1 mL, 12.02 mmol). The mixture was stirred at 130 °C for 40 hours. Upon completion of the reaction, the solution was poured into water. The aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to provide 2-((2S,6R)-2,6-dimethyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purine (1.96 g, 98%) as a yellow solid. LC/MS analysis method 7 ,mass (ES+) m/z 319.2 ^{1}HNMR (DMSO-d_6): 12.37 (1H, s), 7.76 (1H, s), 4.38 (2H, d), 4.12 (4H, brs), 3.69 (4H, m), 3.54 (2H, m), 2.40 (2H, m), 1.14 (6H, d).

c) 8-Bromo-2-((2*S*,6*R*)-2,6-dimethyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purine

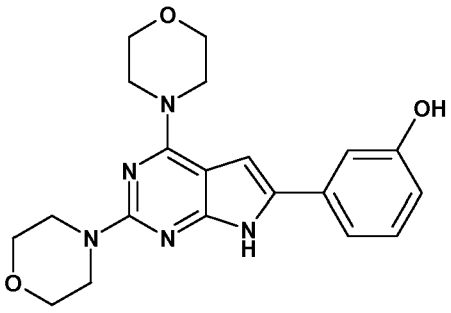
To a solution of 2-((2*S*,6*R*)-2,6-dimethyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purine (860 mg, 2.70 mmol) in CH_2Cl_2(5 mL) was added bromine (0.04 mL, 3.24 mmol). The mixture was stirred at ambient temperature for 3 hours. Saturated sodium thiosulfate was added. The aqueous layer was extracted with dichloromethane two times. Organic layers were combined and dried over Na_2SO_4 and solvent was removed under reduced pressure. The crude was purified by flash column chromatography (0-70% EtOAc/Heptane gradient) to furnish product as an off-white solid (362.1 mg, 34%). LC/MS analysis using method 7, mass (ES+) m/z 399.1 ^{1}HNMR ($CDCl_3$): 4.31 (2H, d), 4.09 (4H, brs), 3.74 (4H, m), 3.59 (2H, m), 2.51 (2H, m), 1.18 (6H, d).

d) 3-[2-((2*S*,6*R*)-2,6-Dimethyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purin-8-yl]-phenol

To a round bottom flask were added, 8-bromo-2-((2*S*,6*R*)-2,6-dimethyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purine (38.2 mg, 0.096 mmol), cesium fluoride 58.4 mg, 0.39 mmol), 3-hydroxyphenylboronic acid (39.8 mg, 0.29 mmol) and tetrakis(triphenylphosphine)palladium (8.9 mg, 7.69 mmol) followed by 1 mL of acetonitrile/water solvent mixture (10/1 ratio). Suspension was heated to 115 °C and stirred overnight. Upon completion of the reaction, the suspension was cooled and solids filtered off. Solvent was removed under reduced pressure and the crude was purified directly by preparative HPLC to provide 3-[2-((2S,6R)-2,6-dimethyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purin-8-yl]-phenol (18.5 mg, 47%) as yellow solid . LC/MS analysis method 7, mass (ES+) m/z 411.2, retention time 1.40 min. ^{1}HNMR ($CDCl_3$): 7.34 (1H, d), 7.24 (2H, m), 6.87 (1H, d), 4.35 (2H, d), 4.30 (4H, brs), 3.80 (4H, m), 3.57(2H, m), 2.53 (2H, t), 1.16 (6H, d).

Example 2

3-(2,4-Di-morpholin-4-yl-7H-pyrrolo[2,3-d]pyrimidin-6-yl)-phenol



a) 2,4-Di-morpholin-4-yl-7H-pyrrolo[2,3-d]pyrimidine

In a 20 mL vial, 2,4-dichloro-7H-pyrrolo[2,3-d]pyrimidine (0.19 g, 1.011 mmol, 1.0 equiv) was dissolved in NMP (2 mL). Di-isopropyl-ethylamine (0.392g, 0.514 mL, 3.03 mmol, 3.0 equiv) and morpholine (0.264 g, 0.264 mL, 3.03 mmol, 3.0 equiv.) were then added. The reaction

mixture was then transferred into a 5 mL microwave vessel and heated at 200˚C for 30 minutes. The reaction was then cooled down to room temperature and diluted with 35 mL of ethyl acetate. The organic phase was then washed with saturated ammonium chloride solution (2 x 30 mL). The organic layer was then dried with $MgSO_4$, filtered and removed under reduced pressure to obtain a brown oil. The oil was then purified using flash chromatography using 20% to 100% gradient of EtOAc/Heptane. The compound was isolated as a white solid (239.1 mg, 82% yield). ^{1}HNMR ($CDCl_3$): δ 9.67(1H, brs), 6.74(1H, m), 6.29(1H, d), 3.82(8H,dt), 3.72 (8 H, m)

b) 4-Di-morpholin-4-yl-7-(2-trimethylsilanyl-ethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidine

A solution of 2,4-di-morpholin-4-yl-7H-pyrrolo[2,3-d]pyrimidine (180 mg, 0.622 mmol, 1.0 equiv) in 25 mL of DMF was cooled to 0˚C using an ice bath under nitrogen atmosphere. Sodium hydride in oil was then added (60 wt%, 34.8 mg, 0.871 mmol, 1.4 equiv) and the reaction was stirred for 1 hr at 0˚C. To the reaction mixture, 2-(chloromethoxy)ethyl)trimethylsilane (154 µL, 145 mg, 0.871 mmol, 1.4 equiv) was added and the reaction was allowed to warm up to room temperature overnight. The reaction was quenched by adding 5mL of H_2O then poured into 30 mL of EtOAc. The organic phase was then washed twice with aqueous saturated ammonium chloride solution (2x 25 mL). The organic layer was then dried with $MgSO_4$, filtered and removed under reduced pressure to obtain dark brown colored oil. The oil was purified by flash chromatography using 0% to 70% EtOAc/Heptane gradient. The product was isolated as a white solid (205 mg, 79% yield). ^{1}HNMR ($CDCl_3$): δ 6.91 (1H, d), 6.46(1H, d), 5.55 (2H, s), 3.94 (8H, dt), 3.82(8H, brs), 3.57 (2H, t), 0.95 (2H, t), 0.00 (9H, s)

c) 3-[2,4-Di-morpholin-4-yl-7-(2-trimethylsilanyl-ethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-phenol

To a 20 mL vial with a septum were added , 4-di-morpholin-4-yl-7-(2-trimethylsilanyl-ethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidine (40 mg, 0.095 mmol, 1 equiv), palladium (II) acetate (2.15 mg, 0.0095 mmol, 0.1 equiv), copper (II) acetate (3.5 mg, 0.019 mmol, 0.2 equiv) and 3-hydroxyphenyl boronic acid (26.3 mg, 0.191 mmol, 2 equiv) followed by acetic acid (5 mL). The reaction was then stirred under 1 atm of air for 15 hours at room temperature. The reaction was cooled to 0˚C and aqueous saturated sodium bicarbonate solution was added slowly to quench the acid. The reaction was then diluted with ethyl acetate (40 mL) and washed with aqueous saturated bicarbonate solution (2x 20 mL). The organic layer was then removed under reduced pressure. The crude product was directly purified using reverse phase preparative HPLC system (5% to 100% H_2O/MeCN gradient with 0.1% TFA in water as modifier). Upon lypholizing the fractions containing the desired

product, a total of 34.6 mg of C2 and C3 arylation product was obtained. The earlier fraction contained the desired C2 arylation product (8.1 mg, 16.9% yield). ^{1}HNMR ($CDCl_3$): δ 7.24 (1H, brs), 7.21 (1H, brs), 6.82 (1H, d), 6.44 (1H, s), 5.50 (2H, s), 3.87 (4H, m), 3.83 (4H, m), 3.79 (11H, m), 0.98 (2H, t), 0.00 (9H, s)

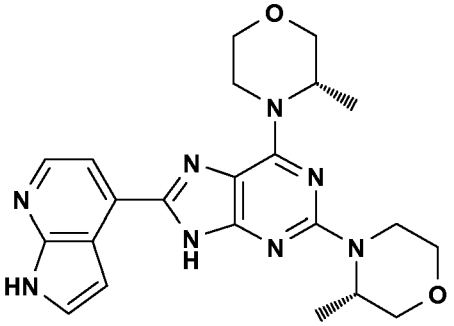
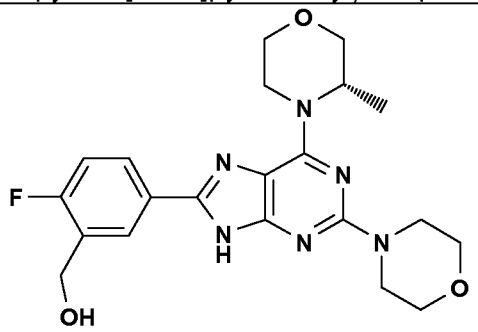
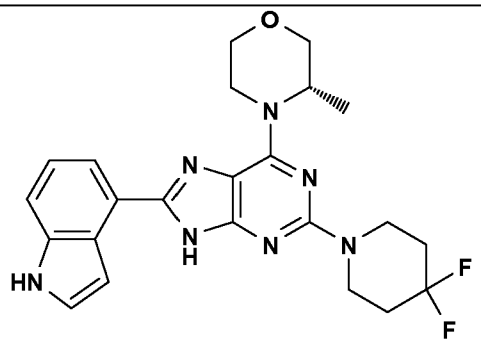
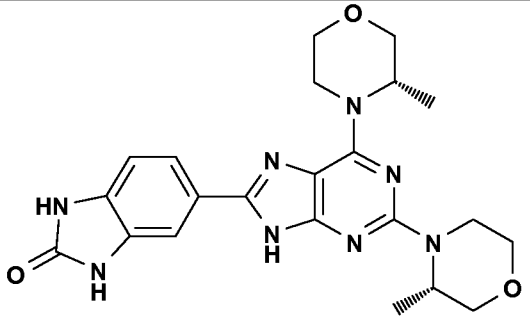
d) 3-(2,4-Di-morpholin-4-yl-7H-pyrrolo[2,3-d]pyrimidin-6-yl)-phenol

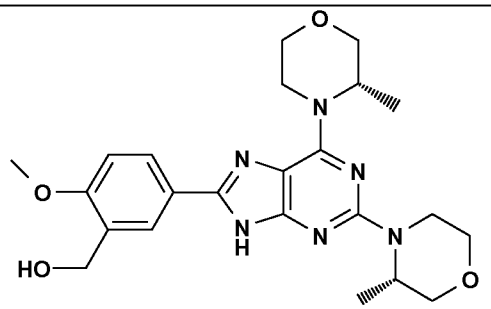
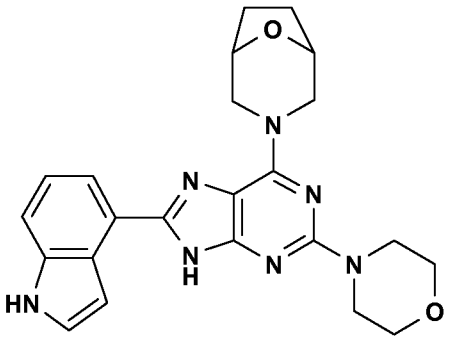
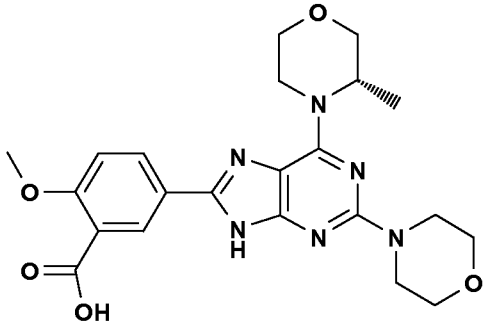
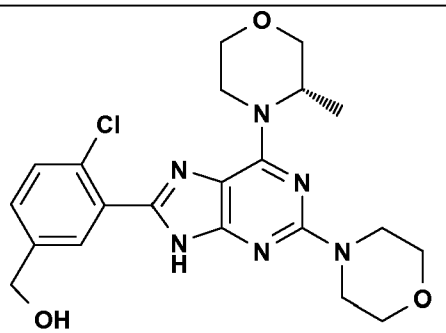
To a round bottom flask were added 3-[2,4-di-morpholin-4-yl-7-(2-trimethylsilanyl-ethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-phenol (8.1 mg, 0.016 mmol) and cesium fluoride (72.4 mg, 0.477 mmol, 30 equiv) followed by acetone (6 mL). The reaction was heated for 6 hours at 40˚C. The reaction was then quenched by adding aqueous saturated ammonium chloride solution (10 mL). Acetone was removed under reduced pressure and the aqueous phase was extracted with DCM (3x 15 mL). The combined organic phase was removed under reduced pressure and the crude product was directly purified using reverse phase preparative HPLC (5% to 70% H_2O/MeCN, with n-propanol in water as modifier) to obtain the desired product as a white solid(4.1mg, 67.8 % yield). LC/MS analysis method 7, mass (ES+) m/z 382.4, retention time 1.05 min ^{1}HNMR ($CDCl_3$): δ 10.15 (1H, brs), 7.15 (1H, t), 7.02 (1H, d), 6.67 (1H, brs), 6.65 (2H, m), 6.52 (1H, s), 3.82 ppm (8H, dt), 3.64 (8H, m)

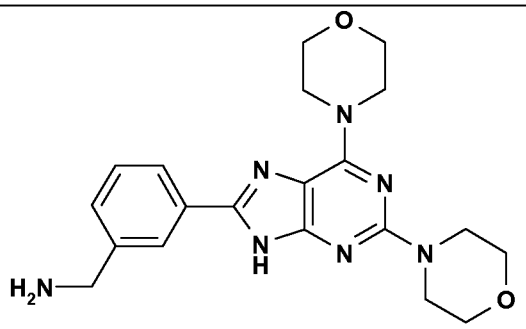
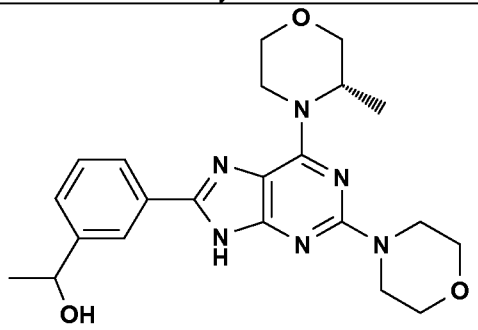
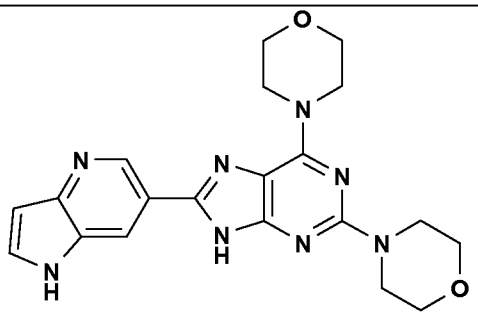
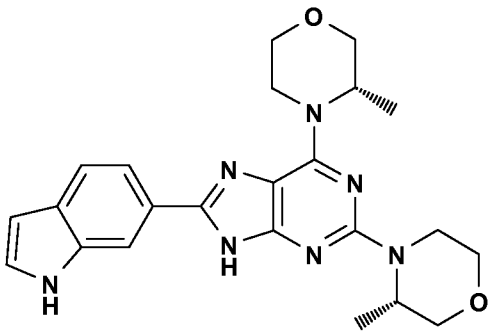
Examples 3 to 38

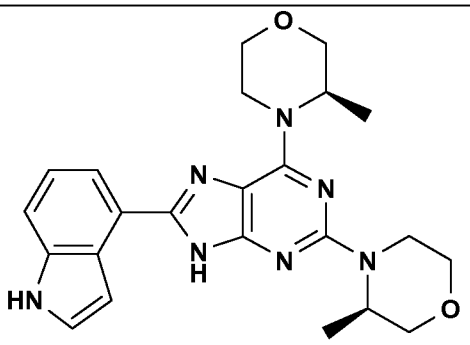
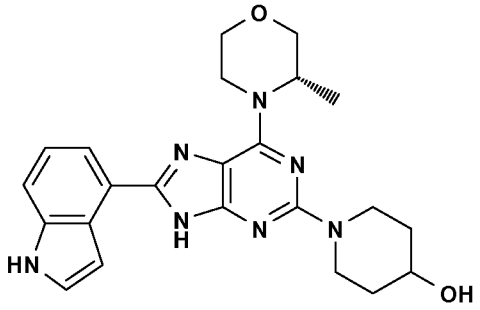
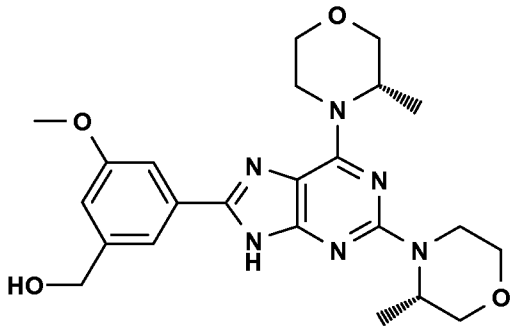
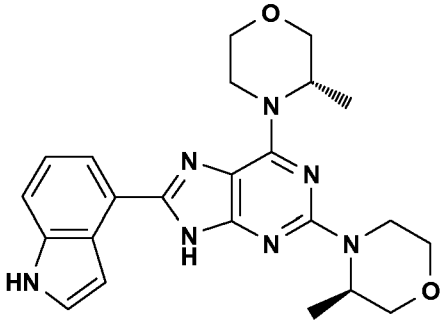
Examples 3 to 38 in Table 2 below can be made using procedures analogous to those described in Examples 1 and 2 using the appropriate boronic acid or boronic ester intermediate.

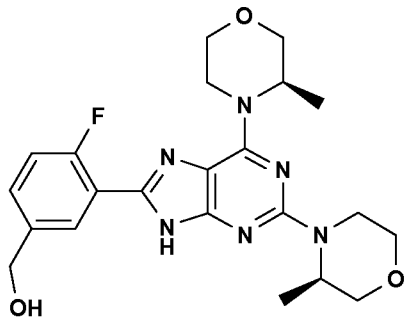
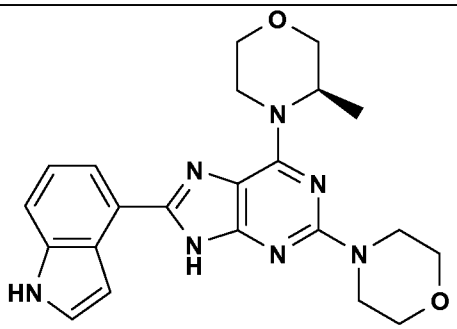
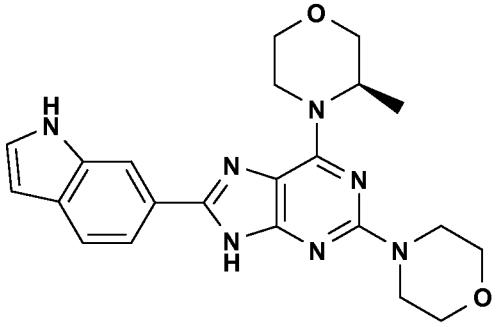
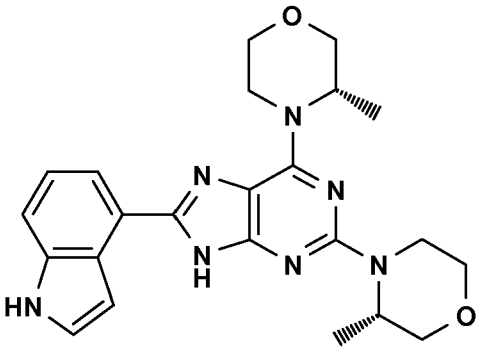
Table 2

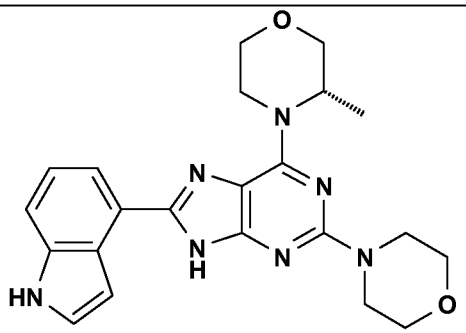
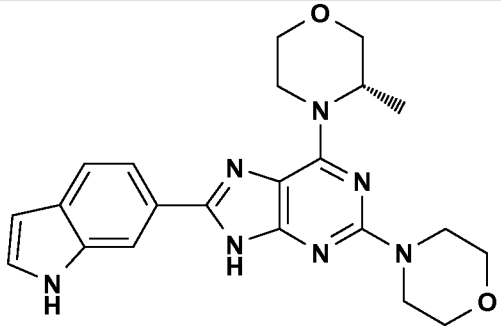
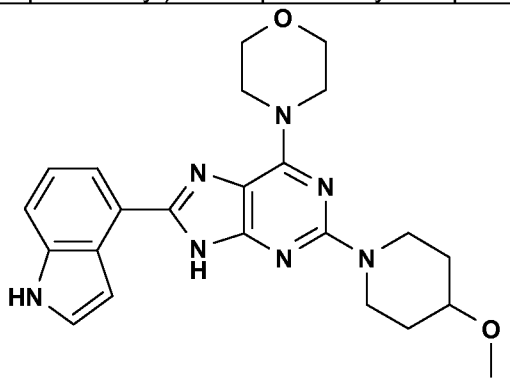
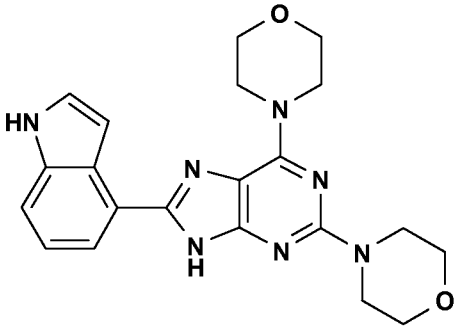
Example Number	Structure and Name	^{1}H NMR	LC/MS
3	 2,6-Bis-((S)-3-methyl-morpholin-4-yl)-8-(1H-pyrrolo[2,3-b]pyridin-4-yl)-9H-purine	^{1}H NMR ($CDCl_3$): 12.66 (1H, s), 8.26 (1H, s), 8.04 (1H, s), 7.62 (1H, s), 7.29 (1H, s), 5.80 (1H, m), 4.58 (2H, m), 4.14-3.98 (3H, m), 3.89-3.53 (6H, m), 3.45-3.34 (2H, m), 1.53 (3H,d), 1.41 (3H, d)	Method 7: C8-BroadRange-Neutral Retention Time: 1.15 min Mass (ES+): 435.5
4	 {2-Fluoro-5-[6-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purin-8-yl]-phenyl}-methanol	^{1}H NMR (CD_3OD): 8.12 (1H, dd), 7.90 (1H, m), 7.17 (1H, t), 5.43 (1H, brs), 5.07 (1H, brs), 4.73 (2H, s), 3.99 (1H, dd), 3.81 (2H, d), 3.75-3.68 (8H, m), 3.66-3.62 (1H, dd), 3.48-3.40 (1H, m), 1.38 (3H, d)	Method 7: C8-BroadRange-Neutral Retention Time: 1.45 min Mass (ES+): 429.3
5	 2-(4,4-Difluoro-piperidin-1-yl)-8-(1H-indol-4-yl)-6-((S)-3-methyl-morpholin-4-yl)-9H-purine	^{1}H NMR (CD_3OD): 7.54 (2H, d), 7.46 (1H, d), 7.35 (1H, m), 7.26 (1H, m), 7.20 (1H, m), 5.51 (1H, brs), 5.10 (1H, brs), 4.02 (1H, dd), 3.94 (4H, m), 3.83 (2H, m), 3.70 (1H, m), 3.50 (1H, m), 1.97 (4H,m), 1.44 (3H, d)	Method 7: C8-BroadRange-Neutral Retention Time: 1.58 min Mass (ES+): 454.3
6	 5-[2,6-Bis-((S)-3-methyl-morpholin-4-yl)-9H-purin-8-yl]-1,3-dihydro-benzoimidazol-2-one	^{1}H NMR (CD_3OD): 7.68 (2H, m), 7.11 (1H, d), 5.40 (1H, brs), 5.05 (1H, brs), 4.66 (1H, m), 4.24 (1H, m), 3.99-3.92 (2H, m), 3.81-3.67 (4H, m), 3.60-3.48 (2H, m), 3.25-3.13 (2H, m), 1.39 (3H,d), 1.25 (3H, d)	Method 7: C8-BroadRange-Neutral Retention Time: 1.02 min Mass (ES+): 451.6

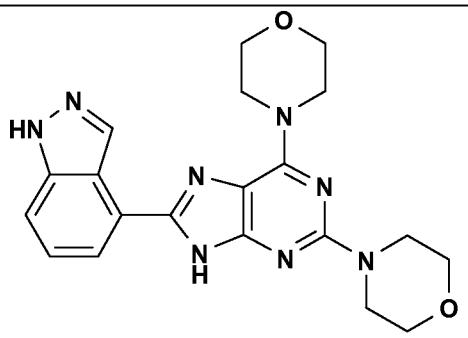
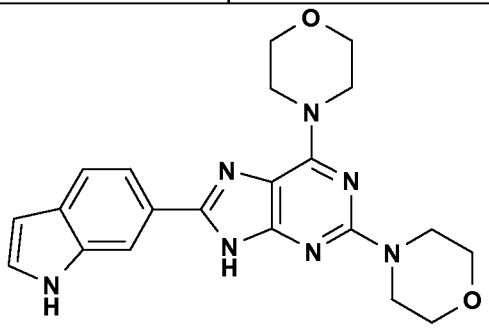
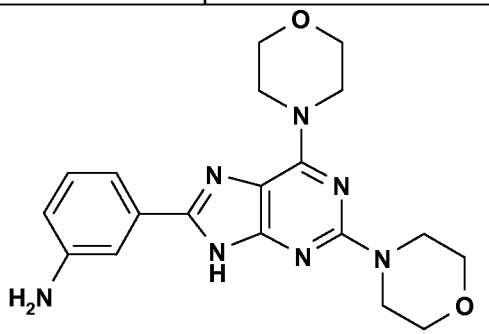
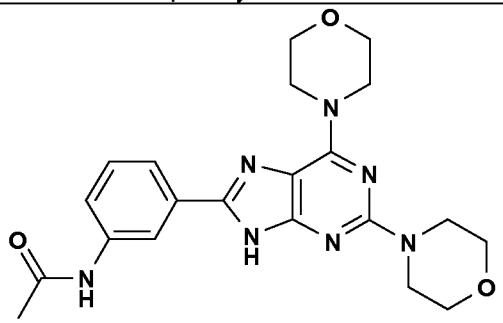
7	 {5-[2,6-Bis-((S)-3-methyl-morpholin-4-yl)-9H-purin-8-yl]-2-methoxy-phenyl}-methanol	^{1}H NMR ($CDCl_3$): 7.88 (2H, m), 6.97 (1H, s), 5.45 (1H, brs), 4.77 (2H, s), 4.58 (1H, brs), 4.21 (1H, brs), 4.08 (1H, brs), 4.07-3.71 (11H, m), 3.56 (2H, m), 3.31 (1H, brs), 1.46 (3H, d),1.33 (3H, d)	Method 7: C8-BroadRange-Neutral Retention Time: 1.09 min Mass (ES+): 455.6
8	 8-(1H-Indol-4-yl)-2-morpholin-4-yl-6-(8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl)-9H-purine	^{1}H NMR (CD_3OD): 7.53 (1H, d), 7.47 (1H, d), 7.36 (1H, d), 7.24 (1H, d), 7.20 (1H, t), 5.17 (2H, brs), 4.50 (2H, s), 3.74 (8H, m), 3.39 (2H, m), 1.95 (4H, m)	Method 7: C8-BroadRange-Neutral Retention Time: 1.16 min Mass (ES+): 432.5
9	 2-Methoxy-5-[6-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purin-8-yl]-benzoic acid	^{1}H NMR (DMSO-d_6): 12.91 (1H, s), 8.25 (1H, s), 8.10 (1H, d), 7.20 (1H, d), 5.34 (1H, brs), 5.00 (1H, brs), 3.98 (1H, m), 3.86 (3H, s), 3.76 (1H, m), 3.72-3.62 (10H, m), 3.56-3.49 (1H, m), 1.29 (3H, d)	Method 7: C8-BroadRange-Neutral Retention Time: 0.99 min Mass (ES+): 455.6
10	 {4-Chloro-3-[6-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purin-8-yl]-phenyl}-methanol	^{1}H NMR (CD_3OD): 7.79 (1H, m), 7.51 (1H, m), 7.44 (1H, m), 5.38 (1H, brs), 4.65 (2H, s), 4.62 (1H, s), 3.99 (1H, dd), 3.79 (2H, m), 3.73 (8H, m), 3.64 (1H, m), 3.41 (1H, m), 1.38 (3H, d)	Method 7: C8-BroadRange-Neutral Retention Time: 1.28 min Mass (ES+): 445.6

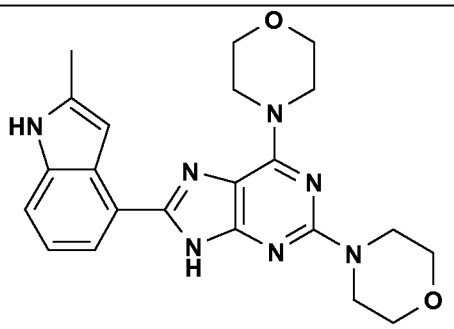
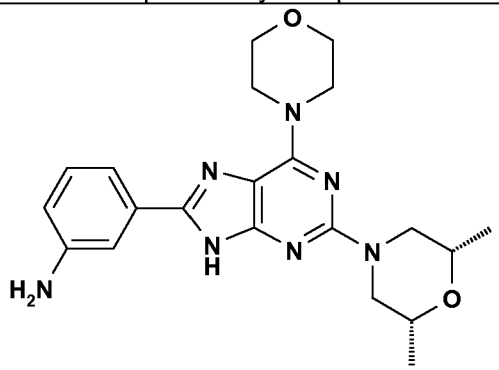
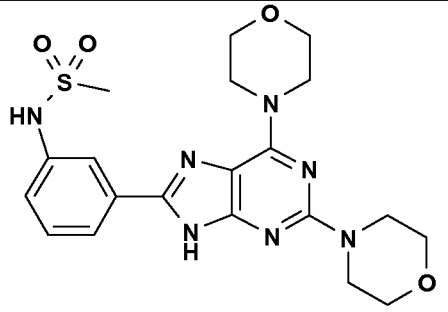
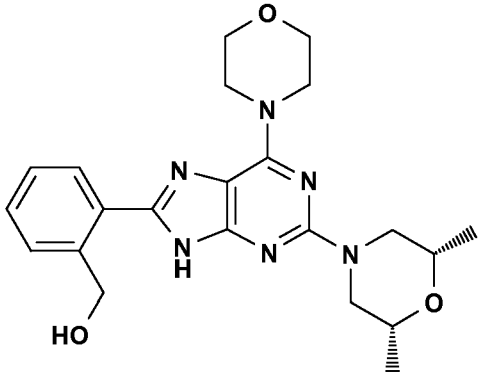
11	 3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-benzylamine	^{1}H NMR (CD_3OD): 8.16 (1H, s), 8.01 (1H, d), 7.58 (1H, t), 7.52 (1H, m), 4.28 (4H, m), 4.20 (2H, s), 3.82 (4H, m), 3.75 (8H, m)	Method 7: C8-BroadRange-Neutral Retention Time: 0.73 min Mass (ES+): 396.5
12	 1-{3-[6-((S)-3-Methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purin-8-yl]-phenyl}-ethanol	^{1}H NMR (CD_3OD): 8.01 (1H, s), 7.86 (1H, m), 7.42 (2H, d), 5.42 (1H, brs), 5.08 (1H, brs), 4.01 (1H, dd), 3.82 (2H, m), 3.73 (8H, m), 3.66 (1H, m), 3.47 (1H, m), 1.49 (3H,d), 1.38 (3H, d)	Method 7: C8-BroadRange-Neutral Retention Time: 1.13 min Mass (ES+): 425.5
13	 2,6-Di-morpholin-4-yl-8-(1H-pyrrolo[3,2-b]pyridin-6-yl)-9H-purine	^{1}H NMR (DMSO-d_6): 13.05 (1H, brs), 11.50 (1H, s), 9.05 (1H, s), 8.37 (1H, s), 7.72 (1H, d), 6.59 (1H, d), 4.20 (4H, brs), 3.75 (4H, m), 3.66 (4H, m), 3.64 (4H, m)	Method 7: C8-BroadRange-Neutral Retention Time: 0.94 min Mass (ES+): 407.4
14	 8-(1H-Indol-6-yl)-2,6-bis-((S)-3-methyl-morpholin-4-yl)-9H-purine	^{1}H NMR (CD_3OD): 8.03 (1H, s), 7.64 (2H, m), 7.33 (1H, d), 6.49 (1H, d), 5.41 (1H, brs), 5.04 (1H, brs), 4.67 (1H, m), 4.26 (1H, dd), 4.01 (1H, dd), 3.94 (1H, dd), 3.82 (2H, s), 3.80-3.65 (3H, m), 3.58-3.43 (2H, m), 3.20 (1H, m), 1.40 (3H,d), 1.26 (3H, d)	Method 7: C8-BroadRange-Neutral Retention Time: 1.30 min Mass (ES+): 434.5

15	 8-(1H-Indol-4-yl)-2,6-bis-((R)-3-methyl-morpholin-4-yl)-9H-purine	^{1}H NMR (CD_3OD): 7.54 (1H, d), 7.47 (1H, d), 7.35 (1H, d), 7.25 (1H, d), 7.20 (1H, t), 5.53 (1H, brs), 5.11 (1H, brs), 4.68 (1H, m), 4.28 (1H, m), 4.03 (1H, m), 3.99 (1H, m), 3.85 (2H, m), 3.73 (3H, m), 3.56 (2H, m), 3.25 (1H, m), 1.45 (3H, d), 1.27 (3H, d)	Method 7: C8-BroadRange-Neutral Retention Time: 1.45 min Mass (ES+): 434.3
16	 1-[8-(1H-Indol-4-yl)-6-((S)-3-methyl-morpholin-4-yl)-9H-purin-2-yl]-piperidin-4-ol	^{1}H NMR (CD_3OD): 7.54 (1H, d), 7.47 (1H, d), 7.35 (1H, d), 7.25 (1H, d), 7.20 (1H, t), 5.50 (1H, brs), 5.11 (1H, brs), 4.45 (2H, m), 4.04 (1H, m), 3.85 (2H, m), 3.81 (1H, m), 3.70 (1H, m), 3.48 (1H, m), 3.18 (2H, m), 1.89 (2H, m), 1.50 (2H, m), 1.45 (3H, d)	Method 7: C8-BroadRange-Neutral Retention Time: 1.28 min Mass (ES+): 434.4
17	 {3-[2,6-Bis-((S)-3-methyl-morpholin-4-yl)-9H-purin-8-yl]-5-methoxy-phenyl}-methanol	^{1}H NMR (CD_3OD): δ 7.57 (1H,s), 7.44 (1H,s), 7.00 (1H,s), 5.40 (1H,brs), 5.07 (1H,brs), 4.67 (1H,m), 4.65 (2H,s), 4.26 (1H,dd), 4.01 (1H,dd), 3.93(1H,dd), 3.87 (3H,s), 3.81 (2H,d), 3.77-3.63 (3H,m), 3.58-3.40 (2H,m), 3.25-3.13 (1H,m), 1.39 (3H,d), 1.25 (3H,d)	Method 7: C8-BroadRange-Neutral Retention Time: 1.30 min Mass (ES+): 455.3
18	 8-(1H-Indol-4-yl)-2-((R)-3-methyl-morpholin-4-yl)-6-((S)-3-methyl-morpholin-4-yl)-9H-purine	^{1}H NMR (CD_3OD): δ 7.54 (1H,d), 7.47 (1H,d), 7.35 (1H,d), 7.24 (1H,d), 7.20 (1H,m), 5.49 (1H,brs), 5.13 (1H,brs), 4.68 (1H,m), 4.26 (1H,dd), 4.04 (1H,dd), 3.95 (3H,m), 3.84 (2H,s), 3.79-3.67 (3H,m), 3.59-3.47 (2H,m), 3.27-3.20 (1H,m), 1.44 (3H,d), 1.27 (3H,d)	Method 7: C8-BroadRange-Neutral Retention Time: 1.21 min Mass (ES+): 434.5

19	 {3-[2,6-Bis-((R)-3-methyl-morpholin-4-yl)-9H-purin-8-yl]-4-fluoro-phenyl}-methanol	^{1}H NMR (CD_3OD): δ 8.09 (1H,dd), 7.42 (1H,m), 7.22 (1H,dd), 5.43 (1H,brs), 5.08 (1H,brs), 4.67 (1H,m), 4.64 (2H,s), 4.27 (1H,dd), 4.01 (1H,dd), 3.94 (1H,dd), 3.81 (2H,s), 3.78-3.63 (3H,m), 3.56-3.41 (2H,m), 3.26-3.13 (1H,m), 1.39 (3H,d), 1.26 (3H, d)	Method 7: C8-BroadRange-Neutral Retention Time: 1.30 min Mass (ES+): 443.4
20	 8-(1H-Indol-4-yl)-6-((R)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purine	^{1}H NMR ($CDCl_3$): δ 10.25 (1H,brs), 8.38 (1H,s), 7.51 (2H,t), 7.39 (1H,t), 7.32 (2H,m), 5.59 (1H,brs), 5.19 (1H,brs), 4.10 (1H,dd), 3.88 (2H,s), 3.84-3.76 (8H,m), 3.71 (1H,m), 3.61 (1H,m), 1,52 (3H,d)	Method 7: C8-BroadRange-Neutral Retention Time: 1.15 min Mass (ES+): 420.5
21	 8-(1H-Indol-6-yl)-6-((R)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purine	^{1}H NMR ($CDCl_3$): δ 11.53 (1H,brs), 8.36 (1H,s), 7.93 (1H,s), 7.71 (1H,m), 7.56 (1H,m), 7.31 (1H,m), 6.60 (1H,s), 5.53 (1H,brs), 5.23 (1H,brs), 4.10 (2H,m), 3.88 (2H,m), 3.74 (1H,m), 3.69 (4H,m), 3.60 (4H,m), 1.58 (3H,d)	Method 7: C8-BroadRange-Neutral Retention Time: 1.19 min Mass (ES+): 420.5
22	 8-(1H-Indol-4-yl)-2,6-bis-((S)-3-methyl-morpholin-4-yl)-9H-purine	^{1}H NMR (CD_3OD): δ 7.54 (1H,d), 7.47 (1H,d), 7.35 (1H,d), 7.24 (1H,d), 7.20 (1H,t), 5.53 (1H, brs), 5.09 (1H,brs), 4.69 (1H,m), 4.27 (1H,dd), 4.04 (1H,dd), 3.96 (1H,dd), 3.85 (2H,s), 3.79-3.07 (3H,m), 3.59-3.49 (2H,m), 3.27-3.13 (1H,m), 1.45(3H,d), 1.27 (3H,d)	Method 7: C8-BroadRange-Neutral Retention Time: 1.20 min Mass (ES+): 434.4

23	 8-(1H-Indol-4-yl)-6-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purine	^{1}H NMR ($CDCl_3$): δ 10.28 (1H,brs), 8.38 (1H,s), 7.50 (2H,d), 7.39 (1H,m), 7.29 (2H,m), 5.60 (1H,brs), 5.20 (1H,brs), 4.11 (1H,dd), 3.88 (2H,s), 3.77 (8H,s), 3.71 (1H,m), 3.60 (1H,m), 1.51 (3H,d)	Method 7: C8-BroadRange-Neutral Retention Time: 1.10 min Mass (ES+): 420.5
24	 8-(1H-Indol-6-yl)-6-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purine	^{1}H NMR ($CDCl_3$): δ 12.19 (1H,brs), 8.47 (1H,s), 7.90 (1H,s), 7.68 (2H,m), 7.29 (1H,m), 6.59 (1H,s), 5.54 (1H,brs), 5.32 (1H,brs), 4.10 (1H,dd), 3.89 (2H,s), 3.77-3.50 (10H,m), 1.49 (3H,m)	Method 7: C8-BroadRange-Neutral Retention Time: 1.40 min Mass (ES+): 420.5
25	 8-(1H-Indol-4-yl)-2-(4-methoxy-piperidin-1-yl)-6-morpholin-4-yl-9H-purine	^{1}H NMR ($CDCl_3$): δ 10.5 (1H,brs), 8.38 (1H,s), 7.50 (2H,t), 7.38 (1H,m), 7.30 (1H,m), 4.40 (3H,m), 4.30 (3H,m), 3.91 (4H,m), 3.46 (1H,m), 3.41 (3H,s), 3.37 (2H,m), 1.97 (2H,m), 1.66 (2H,m)	Method 7: C8-Broadrange Neutral Retention Time: 1.15 min Mass (ES+): 434.5
26	 8-(1H-Indol-4-yl)-2,6-di-morpholin-4-yl-9H-purine	^{1}H NMR (CD_3OD)δ 7.65 (1H,d), 7.62 (1H,d), 7.44 (1H,d), 7.28 (1H,t), 7.12 (1H,d), 4.25 (4H, brs), 3.90 (4H,m), 3.80 (8H,m)	Method 7: C8-Broadrange Neutral Retention Time: 1.3 min Mass (ES+): 406.2

27	 8-(1H-Indazol-4-yl)-2,6-di-morpholin-4-yl-9H-purine	^{1}H NMR (DMSO-d_6)δ 8.70 (1H,s), 7.70 (1H,d), 7.60 (1H,d), 7.40 (1H,t), 7.32 (1H,m), 4.20 (4H,brs), 3.85 (4H,m), 3.65 (8H,m)	Method 7: C8-Broadrange-Neutral Retention Time: 1.2 min Mass (ES+): 407.3
28	 8-(1H-Indol-6-yl)-2,6-di-morpholin-4-yl-9H-purine	^{1}H NMR (DMSO-d_6)δ 8.10 (1H,s), 7.75 (1H,d), 7.60 (1H,d), 7.45 (1H,m), 6.95 (1H,s), 4.19 (4H,brs), 3.75 (4H,m), 3.65 (8H,m)	Method 7: C8-Broadrange-Neutral Retention Time: 1.32 min Mass (ES+): 406.2
29	 3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenylamine	^{1}H NMR (CD_3OD)δ 8.15 (2H,m), 7.67 (1H,t), 7.48 (1H,m), 4.35 (4H,brs), 3.86 (4H,m), 3.80 (8H,brs)	Method 7: C8-Broadrange-Neutral Retention Time: 1.16 min Mass (ES+): 382.3
30	 N-[3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenyl]-acetamide	^{1}H NMR (DMSO-d_6) δ 8.22(1H,s), 7.70 (1H,d), 7.46 (1H,t), 4.20 (4H,brs), 3.75 (4H,m), 3.65 (8H,m), 2.10 (3H,s)	Method 3: C18-General-Neutral Retention Time: 1.22 min Mass (ES+): 424.1

31	 8-(2-Methyl-1H-indol-4-yl)-2,6-di-morpholin-4-yl-9H-purine	^{1}H NMR (DMSO-d_6) δ 7.60 (1H,d), 7.32 (1H,d), 7.05 (1H,t), 6.90 (1H,s), 4.25 (4H,brs), 3.80 (4H,m), 3.65 (8H,m), 2.45 (3H,s)	Method 3: C18-General-Neutral Retention Time: 1.36 min Mass (ES+): 420.3
32	 3-[2-((2S,6R)-2,6-Dimethyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purin-8-yl]-phenylamine	^{1}H NMR (DMSO-d_6) δ 7.85 (1H,brs), 7.80 (1H,m), 7.45 (1H,t), 7.17 (1H,d), 4.42 (2H,d), 4.19 (4H,brs), 3.75 (4H,m), 3.55 (2H,m), 2.45 (2H,m), 1.15 (6H,d)	Method 3: C18-General-Neutral Retention Time: 1.35 min Mass (ES+): 410.3
33	 N-[3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenyl]-methanesulfonamide	^{1}H NMR (DMSO-d_6)δ 7.89 (1H,s), 7.76 (1H,d), 7.43 (1H,t), 7.27 (1H,d), 4.19 (4H,brs), 3.75 (4H,m), 3.65 (8H,m), 3.05 (s, 3H)	Method 3: C18-General-Neutral Retention Time: 1.23 min Mass (ES+): 460.2
34	 {2-[2-((2S,6R)-2,6-Dimethyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purin-8-yl]-phenyl}-methanol	^{1}H NMR ($CDCl_3$) δ 11.0 (1H, brs), 7.70 (1H, m), 7.45 (3H, m), 4.72 (2H, s), 4.41 (2H, d), 4.24 (4H, s), 3.88 (4H, m), 3.57 (2H, m), 2.52 (2H, m), 1.23 (6H, d)	Method 3: C18-General-Neutral Retention Time: 1.43min Mass (ES+): 425.3

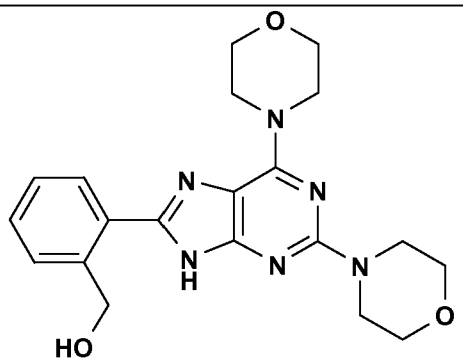
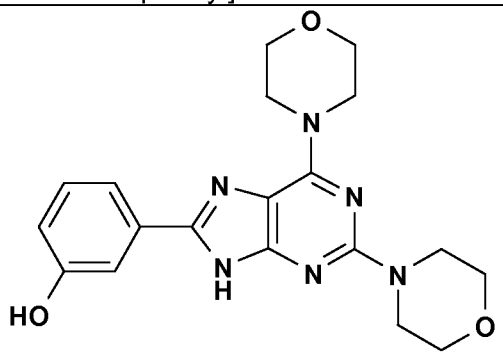
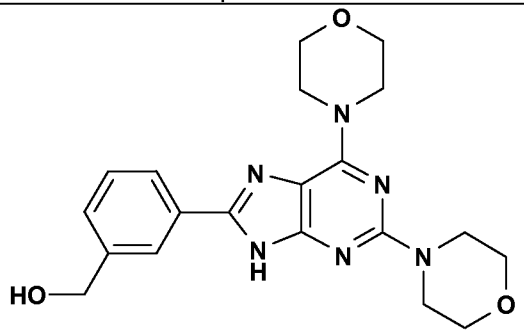
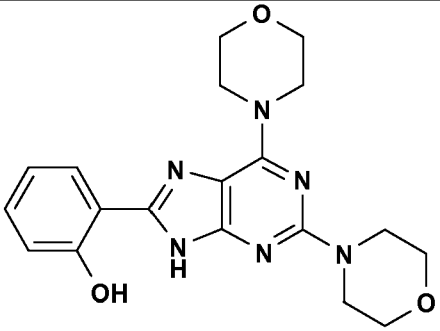
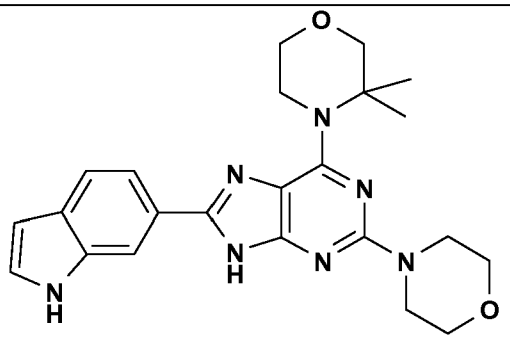
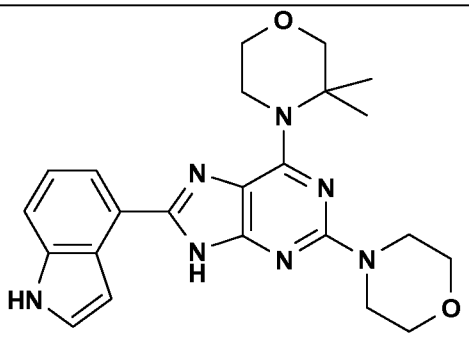
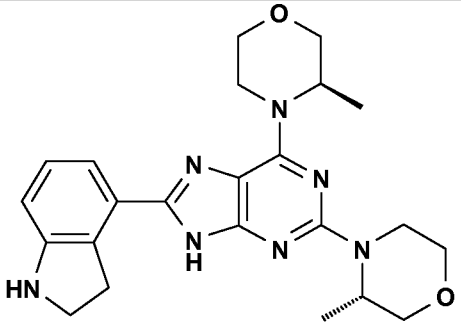
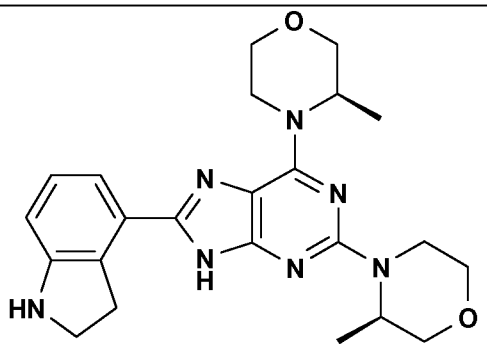
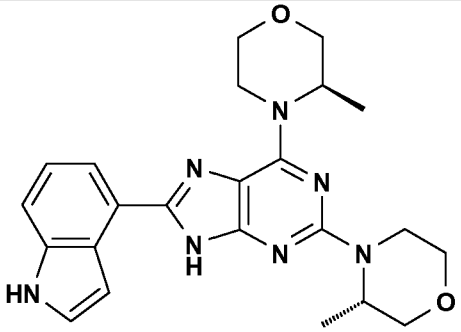
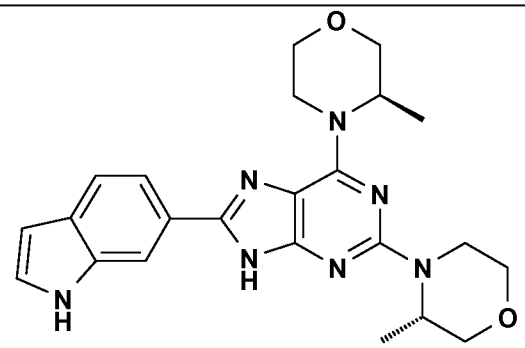
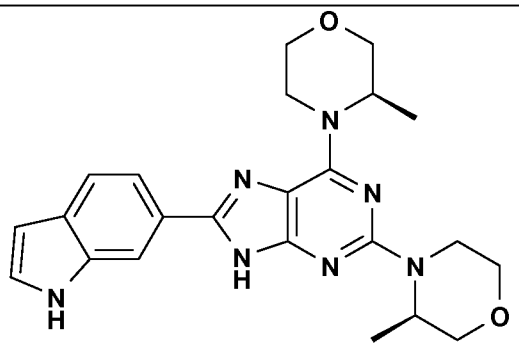
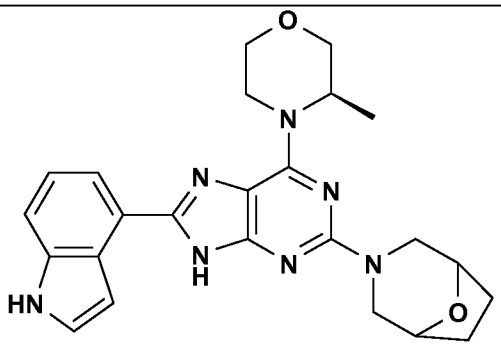
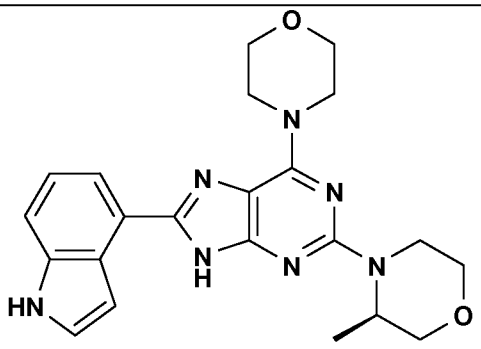
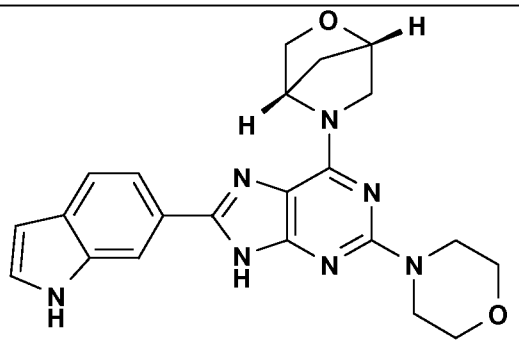
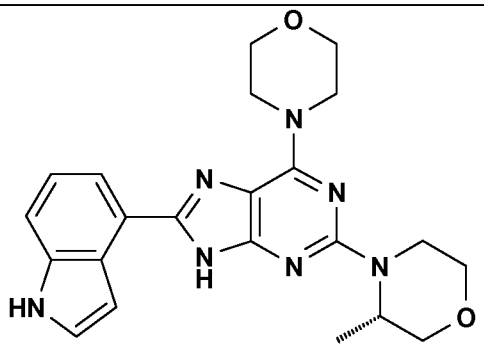
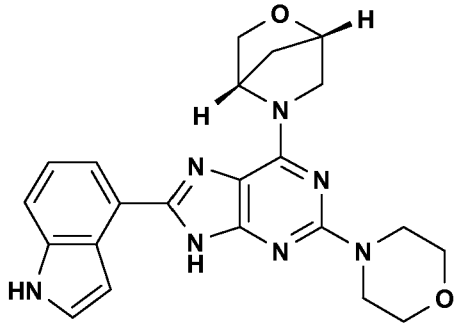
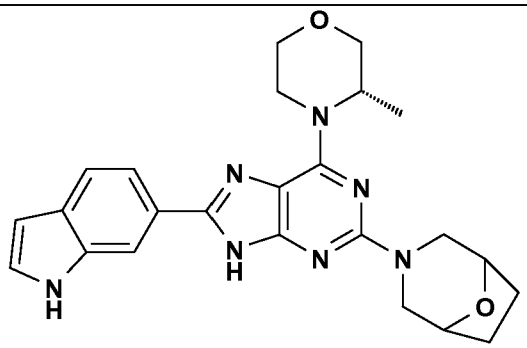
35	 [2-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenyl]-methanol	^{1}H NMR ($CDCl_3$) δ 7.44 (1H, m), 7.19 (3H, m), 4.48 (2H, s), 4.0 (4H, brs) , 3.63 (4H, m), 3.43 (8H, s)	Method 3: C18-General-Neutral Retention Time: 1.22min Mass (ES+): 397.4
36	 3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenol	^{1}H NMR (DMSO-d_6) δ 12.88(1H, brs), 9.59 (1H, s), 7.46 (2H, m), 7.25 (1H, m), 6.79 (1H, m), 4.18 (4H, brs), 3.73 (4H, m), 3.65 (8H, m)	Method 3: C18-General-Neutral Retention Time: 1.18min Mass (ES+): 383.3
37	 [3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenyl]-methanol	^{1}H NMR (DMSO-d_6) δ 12.95(1H, brs), 8.03 (1H, s), 7.90 (1H, d), 7.42 (1H, m), 7.35 (1H, m), 5.27 (1H, t), 4.55 (2H, d) , 4.19 (4H, brs), 3.74 (4H, m), 3.64 (8H, m)	Method 3: C18-General-Neutral Retention Time: 1.15min Mass (ES+): 397.3
38	 2-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenol	^{1}H NMR (CD_3OD) δ 7.77 (1H, d), 7.28 (1H, t), 6.95 (2H, m), 4.55 (1H, brs) , 4.16 (4H, m), 3.82 (4H, m), 3.74 (8H, s)	Method 3: C18-General-Neutral Retention Time: 1.44min Mass (ES+): 383.4

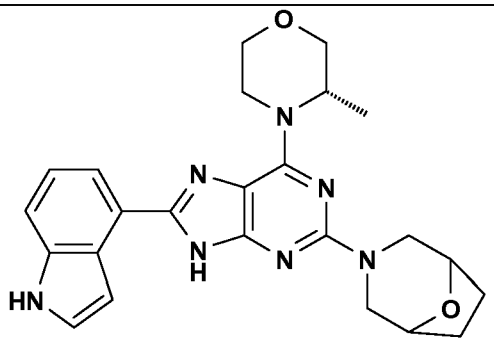
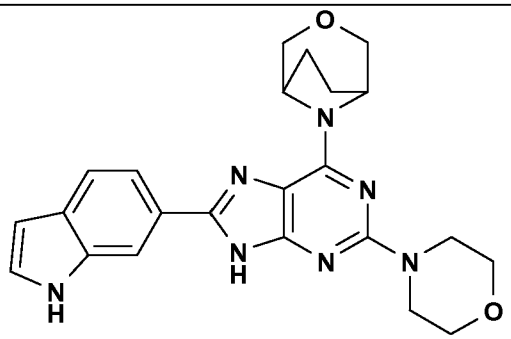
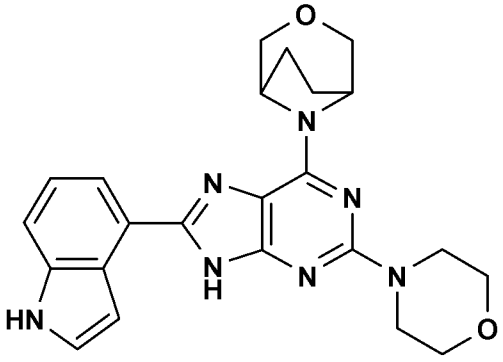
Table 3

Example number	Structure and name	^{1}H NMR	LC/MS
39	 6-(3,3-Dimethyl-morpholin-4-yl)-8-(1H-indol-6-yl)-2-morpholin-4-yl-9H-purine	^{1}H NMR (CD_3OD): 8.04(1H, s), 7.64(2H, m), 7.34(1H, d), 6.49(1H, d), 4.34(2H, m),4.01(2H,m), 3.77(8H, s), 3.52(2H, s), 1.60(6H, s)	Method 7: C8-Broadrange-Neutral Retention Time:1.18 min Mass (ES+): 434
40	 6-(3,3-Dimethyl-morpholin-4-yl)-8-(1H-indol-4-yl)-2-morpholin-4-yl-9H-purine	^{1}H NMR (CD_3OD): 7.55(1H, d), 7.49(1H, d), 7.36(1H, d), 7.20(2H, m), 4.49(2H, m), 4.03(2H, m), 3.77(8H, s), 3.53(2H, s), 1.62(6H, s)	Method 7: C8-Broadrange-NeutralRetention Time:1.12 min Mass (ES+): 434.5
41	 8-(2,3-Dihydro-1H-indol-4-yl)-2-((S)-3-methyl-morpholin-4-yl)-6-((R)-3-methyl-morpholin-4-yl)-9H-purine	^{1}H NMR (CD_3OD): 7.87(1H, d), 7.53(1H, t), 7.43(1H, d), 5.42(1H, brs), 5.05(1H, brs), 4.60(1H, m), 4.17(1H, d), 4.02(2H, m), 3.40-3.90(12H, m),1.45(3H, d), 1.32(3H, d)	Method 7: C8-Broadrange-NeutralRetention Time:1.30 min Mass (ES+): 436.6

42	 8-(2,3-Dihydro-1H-indol-4-yl)-2,6-bis-((R)-3-methyl-morpholin-4-yl)-9H-purine	^{1}H NMR (CD_3OD): 7.88(1H, d), 7.54(1H, t), 7.44(1H, d), 5.48(1H, brs), 5.05(1H, brs), 4.58(1H, m), 4.20(1H, m), 4.01(2H, m), 3.37-3.88(12H, m), 1.46(3H, d), 1.33(3H,d)	Method 7: C8-Broadrange-Neutral Retention Time:1.30 min Mass (ES+): 436.6
43	 8-(1H-Indol-4-yl)-2-((S)-3-methyl-morpholin-4-yl)-6-((R)-3-methyl-morpholin-4-yl)-9H-purine	^{1}H NMR (CD_3OD): 7.54(1H, m), 7.47(1H, m), 7.36(1H, d), 7.24(1H, m), 7.20(1H, m), 5.49(1H, brs), 5.12(1H, brs), 4.68(1H, m), 4.27(1H, m), 4.03(1H, m), 3.95(1H, m), 3.85(2H, s), 3.76(3H, m), 3.56(2H, m), 3.24(1H, m), 1.44(3H, d), 1.27(3H, d)	Method 7:8-Broadrange-Neutral Retention Time:1.12 min Mass (ES+): 434.5
44	 8-(1H-Indol-6-yl)-2-((S)-3-methyl-morpholin-4-yl)-6-((R)-3-methyl-morpholin-4-yl)-9H-purine	^{1}H NMR (CD_3OD): 8.03(1H, s), 7.64(2H, m), 7.32(1H, s), 6.48(1H, s), 5.38(1H, brs), 5.08(1H, brs), 4.67(1H, m), 4.24(1H, m), 3.97(2H, m), 3.83(2H, s), 3.73(3H, m), 3.55(2H, m), 3.20(1H, m), 1.39(3H, d), 1.26(3H, d)	Method 7: C8-Broadrange-NeutralRetention Time:1.18 min Mass (ES+): 434.5

45	 8-(1H-Indol-6-yl)-2,6-bis-((R)-3-methyl-morpholin-4-yl)-9H-purine	^{1}H NMR (CD_3OD): 8.03(1H, s), 7.63(2H, m), 7.32(1H, d), 6.48(1H, d), 5.41(1H, brs), 5.07(1H, brs), 4.67(1H, m),4.26(1H, m), 3.99(2H, m), 3.83(2H, s), 3.73(3H, m), 3.55(2H, m), 3.23(1H, m), 1.40(3H, d), 1.26(3H, d)	Method 7: C8-Broadrange-Neutral Retention Time:1.27 min Mass (ES+): 434.4
46	 8-(1H-Indol-4-yl)-6-((R)-3-methyl-morpholin-4-yl)-2-(8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl)-9H-purine	^{1}H NMR (CD_3OD): 7.54(1H, d), 7.47(1H, d), 7.35(1H, d), 7.24(1H, d), 7.20(1H, m), 5.53(1H, brs), 5.11(1H, brs), 4.43(2H, s), 4.25(2H, d), 4.04(1H, m), 3.84(2H, m), 3.70(1H, m),3.48(1H, m), 3.10(2H, m), 1.88(4H, m), 1.44(3H, d)	Method 7: C8-Broadrange-Neutral Retention Time:1.21 min Mass (ES+): 446.5
47	 8-(1H-Indol-4-yl)-2-((R)-3-methyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purine	^{1}H NMR (CD_3OD): 7.53(1H, d), 7.49(1H, d), 7.35(1H, d), 7.20(2H, m),4.69(1H, m),4.31(5H, m)3.94(1H, m), 3.85(4H, m),3.75(2H, m),3.55(1H, m), 3.24(1H, m), 1.27(3H, d)	Method 7: C8-Broadrange-NeutralRetention Time:1.17 min Mass (ES+): 420.5

48	 8-(1H-Indol-6-yl)-2-morpholin-4-yl-6-(1S,4S)-2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl-9H-purine	^{1}H NMR (CD_3OD): 8.04(1H, s), 7.64(2H, m), 7.33(1H, d), 6.49(1H, d), 4.75(1H, s), 3.93(2H,m), 3.74(11H, m), 2.04(2H, s)	Method 7: C8-Broadrange-Neutr Retention Time:1.23 min Mass (ES+): 418.2
49	 8-(1H-Indol-4-yl)-2-((S)-3-methyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purine	^{1}H NMR (CD_3OD): 8.04(1H, s), 7.63(2H, m), 7.33(1H, d), 6.48(1H, d), 4.68(1H, m), 4.24(5H, m), 3.94(1H,m), 3.83(4H,m), 3.74(2H,m), 3.56(1H,m), 3.23(1H, m), 1.26(3H, d)	Method 7: C8-Broadrange-NeutralRetention Time:1.22 min Mass (ES+): 420.5
50	 8-(1H-Indol-4-yl)-2-morpholin-4-yl-6-(1S,4S)-2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl-9H-purine	^{1}H NMR (CD_3OD): 7.54(1H, d), 7.48(1H, d), 7.36(1H, d), 7.26(1H, m), 7.20(1H, t), 4.77(1H, s), 3.97(3H, m), 3.75(10H, m), 2.07(2H, s)	Method 7: C8-Broadrange-Neutral Retention Time:1.19 min Mass (ES+): 418.3
51	 8-(1H-Indol-6-yl)-6-((S)-3-methyl-morpholin-	^{1}H NMR (CD_3OD): 7.93(1H, s), 7.53(2H, m), 7.23(1H, d), 6.39(1H, d), 5.31(1H, brs), 4.95(1H, brs), 4.32(2H, s), 4.14(2H, d), 3.91(1H, m), 3.73(2H, s), 3.58(1H, m), 3.37(1H, m),	Method 7: C8-Broadrange-Neutral Retention Time:1.37min Mass (ES+): 446.4

	4-yl)-2-(8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl)-9H-purine	3.00(2H, d), 1.70(4H, m), 1.29(3H, d)	
52	 8-(1H-Indol-4-yl)-6-((S)-3-methyl-morpholin-4-yl)-2-(8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl)-9H-purine	^{1}H NMR (CD_3OD): 7.54(1H, d), 7.47(1H, d), 7.35(1H, d), 7.24(1H, d), 7.20(1H, t), 5.52(1H, brs), 5.09(1H, brs), 4.43(2H, s), 4.27(2H, d), 4.03(1H, m), 3.85(2H, s), 3.70(1H, m), 3.48(1H, m), 3.09(2H, d), 1.88(4H, m), 1.45(3H, d)	Method 7: C8-Broadrange-Neutral Retention Time:1.22 min Mass (ES+): 446.5
53	 8-(1H-Indol-6-yl)-2-morpholin-4-yl-6-(3-oxa-8-aza-bicyclo[3.2.1]oct-8-yl)-9H-purine	^{1}H NMR (CD_3OD): 8.04(1H, s), 7.63(2H, m), 7.33(1H, d), 6.49(1H, d), 5.30(2H, brs), 3.88(2H, d), 3.74(8H, m), 3.67(2H, d), 2.12(4H, m)	Method 7: C8-Broadrange-Neutral Retention Time:1.32 min Mass (ES+): 432.4
54	 8-(1H-Indol-4-yl)-2-morpholin-4-yl-6-(3-oxa-8-aza-bicyclo[3.2.1]oct-8-yl)-9H-purine	^{1}H NMR (CD_3OD): 7.55(1H, d), 7.48(1H, d), 7.36(1H, d), 7.20(2H, m), 5.37(2H, brs), 3.92(2H, d), 3.70(2H, d), 2.15(4H, m)	Method 7: C8-Broadrange-Neutral Retention Time:1.18 min Mass (ES+): 432.5

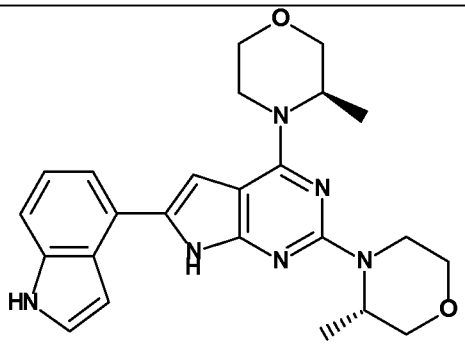
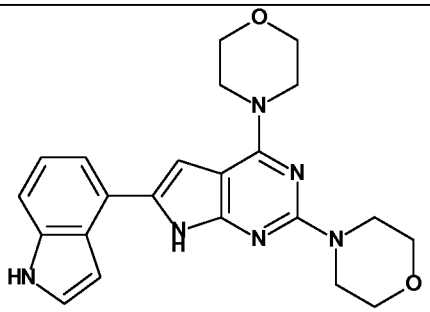
55	 6-(1H-Indol-4-yl)-4-((R)-3-methyl-morpholin-4-yl)-2-((S)-3-methyl-morpholin-4-yl)-7H-yrrolo[2,3-d]pyrimi dine	^{1}H NMR (DMSO-d_6): 11.66(1H, brs), 11.26(1H, br), 7.44(1H, t), 7.35(2H, m), 7.12(1H, t), 6.84(1H, d), 4.74(1H, brs), 4.55(1H, brs), 4.41(1H, t), 4.14(1H, t), 3.99(1H, d), 3.92(1H, d) 3.75(3H, m), 3.51(4H, m), 3.16 (1H, m), 1.32 (3H, t), 1.20 (3H, m)	Method 7: C8-Broadrange-Neutral Retention Time:1.17 min Mass (ES+): 433.5
56	 6-(1H-Indol-4-yl)-2,4-di-morpholin- 4-yl-7H-pyrrolo[2,3-d]pyrimidine	^{1}H NMR (DMSO-d_6): 11.52(1H, brs), 11.26(1H, brs), 7.42(1H, brs), 7.34(2H, m), 7.1(1H, t), 6.85(2H, brs), 3.85(4H, m), 3.75(4H, m) 3.66(8H, m),	Method 7: C8-Broadrange-Neutral Retention Time:1.03 min Mass (ES+): 405.5

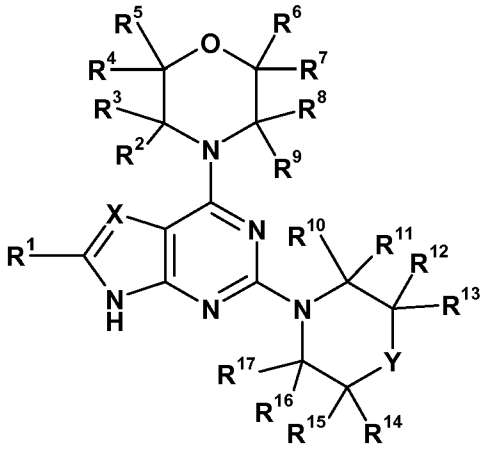
Table 4.

Example Number	Test 1: PI3Kα IC_{50} (nM)	Test 2: mTOR IC_{50} (nM)	Test 3: TSC1-/- IC50 (nM)	Test 4: Autophagy EC_{50}
39	2530	160	146	2317
40	6470	350	841	>8000
41	3350	30	457	2901
42	4910	40	99	4627
43	1010	40	39	160
44	5950	140	388	395
45	7080	650	989	>400
46	580	30	100	171
47	60	60	111	461
48	4300	1010	1463	6410
49	4430	370	678	>500
50	4220	1200	920	8673
51	5940	220	228	284
52	420	50	88	386
53	>9100	190	528	782
54	5790	150	309	1253
55	1440	2670	71	1000
56	2010	2390	174	3651

5

Claims

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof,

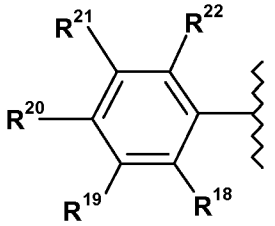


(I)

wherein

X represents N or CH;

R^1 represents



wherein

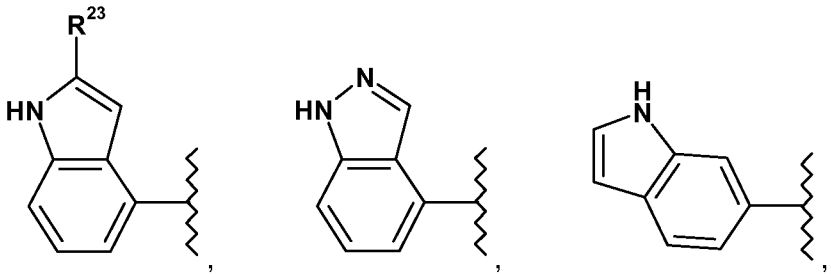
R^{18} and R^{22} independently represent hydrogen, halogen, hydroxy or hydroxy-C_{1-3}alkyl-;

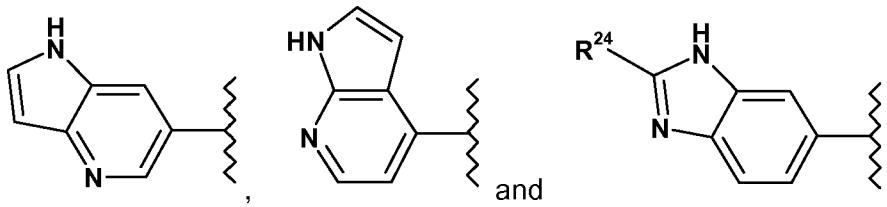
R^{19} and R^{21} independently represent hydrogen, amino, hydroxy, carboxy, C_{1-3}alkoxy, amino-C_{1-3}alkyl-, C_{1-3}alkyl-C(=O)-NH-, C_{1-3}alkyl-$S(=O)_m$-NH- or hydroxy-C_{1-3}alkyl-;

m represents 0, 1 or 2;

R^{20} represents hydrogen, halogen or C_{1-3}alkoxy; or

R^1 is selected from the group consisting of





wherein

R^{23} represents hydrogen or methyl;

R^{24} represents hydrogen, oxo or C_{1-3}alkyl;

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} independently represent hydrogen or methyl;

or R^2 and R^8 together form an ethylene bridge;

or R^2 and R^6 together form a methylene bridge;

or R^{12} and R^{14} together form an ethylene bridge; and

Y represents O, CHR^{25} or $CR^{26}R^{27}$

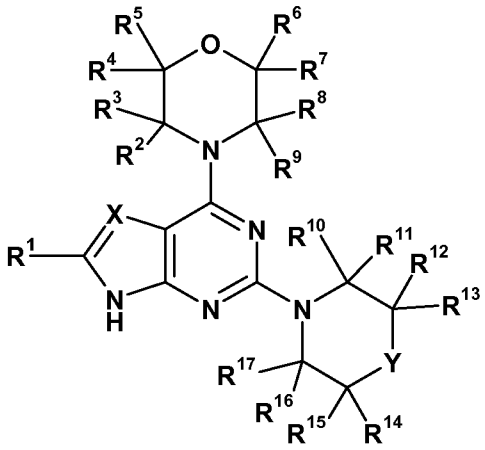
wherein

R^{25} represents hydroxy or C_{1-3}alkoxy; and

R^{26} and R^{27} independently represent hydrogen or halogen;

with the proviso that the compound of formula (I) is other than 2,6-di-morpholin-4-yl-8-phenyl-9H-purine.

2. A compound of formula (I), or a pharmaceutically acceptable salt thereof,

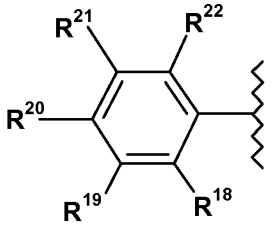


(I)

wherein

X represents N or CH;

R^1 represents



wherein

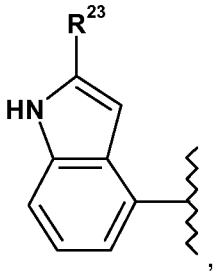
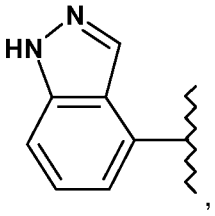
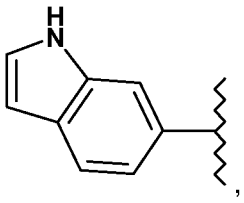
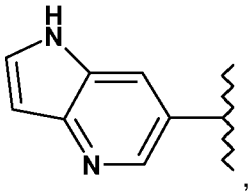
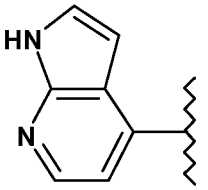
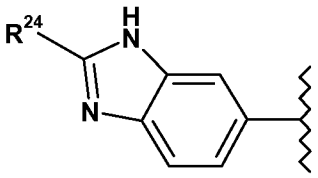
R^{18} and R^{22} independently represent hydrogen, halogen, hydroxy or hydroxy-C_{1-3}alkyl-;

R^{19} and R^{21} independently represent hydrogen, amino, hydroxy, carboxy, C_{1-3}alkoxy, amino-C_{1-3}alkyl-, C_{1-3}alkyl-C(=O)-NH-, C_{1-3}alkyl-$S(=O)_m$-NH- or hydroxy-C_{1-3}alkyl-;

m represents 0, 1 or 2;

R^{20} represents hydrogen, halogen or C_{1-3}alkoxy; or

R^1 is selected from the group consisting of

, , , ,  and 

wherein

R^{23} represents hydrogen or methyl;

R^{24} represents hydrogen, oxo or C_{1-3}alkyl;

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} independently represent hydrogen or methyl; or R^5 and R^6 together form an ethylene bridge; and

Y represents O, CHR^{25} or $CR^{26}R^{27}$

wherein

R^{25} represents hydroxy or C_{1-3}alkoxy; and

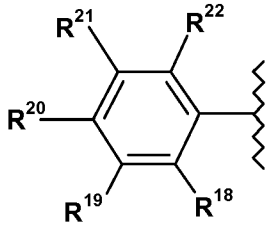
R^{26} and R^{27} independently represent hydrogen or halogen;

with the proviso that the compound of formula (I) is other than 2,6-di-morpholin-4-yl-8-phenyl-9H-purine.

3. A compound according to Claim 1 or Claim 2, or a pharmaceutically acceptable salt thereof, wherein X represents N.

4. A compound according to Claim 1 or Claim 2, or a pharmaceutically acceptable salt thereof, wherein X represents CH.

5. A compound according to any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R^1 represents



wherein

R^{18} and R^{22} independently represent hydrogen, halogen, hydroxy or hydroxy-C_{1-3}alkyl-;

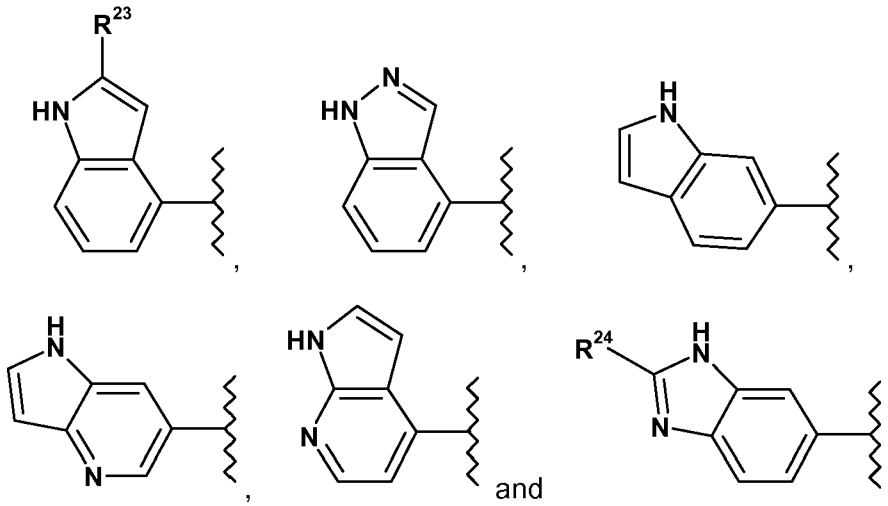
R^{19} and R^{21} independently represent hydrogen, amino, hydroxy, carboxy, C_{1-3}alkoxy, amino-C_{1-3}alkyl-, C_{1-3}alkyl-C(=O)-NH-, C_{1-3}alkyl-$S(=O)_m$-NH- or hydroxy-C_{1-3}alkyl-;

m represents 0, 1 or 2; and

R^{20} represents hydrogen, halogen or C_{1-3}alkoxy.

6. A compound according to Claim 5, or a pharmaceutically acceptable salt thereof, wherein at least one of R^{18}, R^{19}, R^{20}, R^{21} and R^{22} is not hydrogen

7. A compound according to any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from the group consisting of



and

wherein

R^{23} represents hydrogen or methyl; and

R^{24} represents hydrogen, oxo or C_{1-3}alkyl.

8. A compound according to any one of Claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein Y represents O;

9. A compound according to any one of Claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein Y represents CHR^{26} or $CR^{27}R^{28}$.

10. A compound according to Claim 1 or Claim 2, which is selected from:
3-[2-((2S,6R)-2,6-Dimethyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purin-8-yl]-phenol;
3-(2,4-dimorpholino-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenol;
2,6-Bis-((S)-3-methyl-morpholin-4-yl)-8-(1H-pyrrolo[2,3-b]pyridin-4-yl)-9H-purine;
{2-Fluoro-5-[6-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purin-8-yl]-phenyl}-methanol;
2-(4,4-Difluoro-piperidin-1-yl)-8-(1H-indol-4-yl)-6-((S)-3-methyl-morpholin-4-yl)-9H-purine;
5-[2,6-Bis-((S)-3-methyl-morpholin-4-yl)-9H-purin-8-yl]-1,3-dihydro-benzoimidazol-2-one;
{5-[2,6-Bis-((S)-3-methyl-morpholin-4-yl)-9H-purin-8-yl]-2-methoxy-phenyl}-methanol;
8-(1H-Indol-4-yl)-2-morpholin-4-yl-6-(8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl)-9H-purine;
2-Methoxy-5-[6-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purin-8-yl]-benzoic acid;
{4-Chloro-3-[6-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purin-8-yl]-phenyl}-methanol;
3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-benzylamine;
1-{3-[6-((S)-3-Methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purin-8-yl]-phenyl}-ethanol;
2,6-Di-morpholin-4-yl-8-(1H-pyrrolo[3,2-b]pyridin-6-yl)-9H-purine;
8-(1H-Indol-6-yl)-2,6-bis-((S)-3-methyl-morpholin-4-yl)-9H-purine;
8-(1H-Indol-4-yl)-2,6-bis-((R)-3-methyl-morpholin-4-yl)-9H-purine;
1-[8-(1H-Indol-4-yl)-6-((S)-3-methyl-morpholin-4-yl)-9H-purin-2-yl]-piperidin-4-ol;
{3-[2,6-Bis-((S)-3-methyl-morpholin-4-yl)-9H-purin-8-yl]-5-methoxy-phenyl}-methanol;
8-(1H-Indol-4-yl)-2-((R)-3-methyl-morpholin-4-yl)-6-((S)-3-methyl-morpholin-4-yl)-9H-purine;
{3-[2,6-Bis-((R)-3-methyl-morpholin-4-yl)-9H-purin-8-yl]-4-fluoro-phenyl}-methanol;
8-(1H-Indol-4-yl)-6-((R)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purine;
8-(1H-Indol-6-yl)-6-((R)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purine;
8-(1H-Indol-4-yl)-2,6-bis-((S)-3-methyl-morpholin-4-yl)-9H-purine;
8-(1H-Indol-4-yl)-6-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purine;
8-(1H-Indol-6-yl)-6-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-9H-purine;
8-(1H-Indol-4-yl)-2-(4-methoxy-piperidin-1-yl)-6-morpholin-4-yl-9H-purine;
8-(1H-Indol-4-yl)-2,6-di-morpholin-4-yl-9H-purine;

8-(1H-Indazol-4-yl)-2,6-di-morpholin-4-yl-9H-purine;
8-(1H-Indol-6-yl)-2,6-di-morpholin-4-yl-9H-purine;
3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenylamine;
N-[3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenyl]-acetamide;
8-(2-Methyl-1H-indol-4-yl)-2,6-di-morpholin-4-yl-9H-purine;
3-[2-((2S,6R)-2,6-Dimethyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purin-8-yl]-phenylamine;
N-[3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenyl]-methanesulfonamide;
{2-[2-((2S,6R)-2,6-Dimethyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purin-8-yl]-phenyl}-methanol;
[2-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenyl]-methanol;
3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenol;
[3-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenyl]-methanol;
2-(2,6-Di-morpholin-4-yl-9H-purin-8-yl)-phenol;
6-(3,3-Dimethyl-morpholin-4-yl)-8-(1H-indol-6-yl)-2-morpholin-4-yl-9H-purine;
6-(3,3-Dimethyl-morpholin-4-yl)-8-(1H-indol-4-yl)-2-morpholin-4-yl-9H-purine;
8-(2,3-Dihydro-1H-indol-4-yl)-2-((S)-3-methyl-morpholin-4-yl)-6-((R)-3-methyl-morpholin-4-yl)-9H-purine;
8-(2,3-Dihydro-1H-indol-4-yl)-2,6-bis-((R)-3-methyl-morpholin-4-yl)-9H-purine;
8-(1H-Indol-4-yl)-2-((S)-3-methyl-morpholin-4-yl)-6-((R)-3-methyl-morpholin-4-yl)-9H-purine;
8-(1H-Indol-6-yl)-2-((S)-3-methyl-morpholin-4-yl)-6-((R)-3-methyl-morpholin-4-yl)-9H-purine;
8-(1H-Indol-6-yl)-2,6-bis-((R)-3-methyl-morpholin-4-yl)-9H-purine;
8-(1H-Indol-4-yl)-6-((R)-3-methyl-morpholin-4-yl)-2-(8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl)-9H-purine;
8-(1H-Indol-4-yl)-2-((R)-3-methyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purine;
8-(1H-Indol-6-yl)-2-morpholin-4-yl-6-(1S,4S)-2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl-9H-purine;
8-(1H-Indol-4-yl)-2-((S)-3-methyl-morpholin-4-yl)-6-morpholin-4-yl-9H-purine;
8-(1H-Indol-4-yl)-2-morpholin-4-yl-6-(1S,4S)-2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl-9H-purine;
8-(1H-Indol-6-yl)-6-((S)-3-methyl-morpholin-4-yl)-2-(8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl)-9H-purine;
8-(1H-Indol-4-yl)-6-((S)-3-methyl-morpholin-4-yl)-2-(8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl)-9H-purine;
8-(1H-Indol-6-yl)-2-morpholin-4-yl-6-(3-oxa-8-aza-bicyclo[3.2.1]oct-8-yl)-9H-purine;
8-(1H-Indol-4-yl)-2-morpholin-4-yl-6-(3-oxa-8-aza-bicyclo[3.2.1]oct-8-yl)-9H-purine;
6-(1H-Indol-4-yl)-4-((R)-3-methyl-morpholin-4-yl)-2-((S)-3-methyl-morpholin-4-yl)-7H-yrrolo[2,3-d]pyrimidine;
6-(1H-Indol-4-yl)-2,4-di-morpholin- 4-yl-7H-pyrrolo[2,3-d]pyrimidine;

and pharmaceutically acceptable salts thereof.

11. A compound according to any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, for use as a medicament.

12. A compound according to any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, for use in the treatment or prevention of cancer or a neurodegenerative disorder.

13. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, diluent or carrier

14. The use of a compound according to any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of cancer or a neurodegenerative disorder.

15. A combination comprising a therapeutically effective amount of a compound according to any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, and a second drug substance, for simultaneous or sequential administration.