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(54) **Title**: COMBINATIONS FOR THE TREATMENT OF CANCER

(57) **Abstract**: The present invention relates to combinations of at least two compounds A and B, compound A being an inhibitor of Mps-1 kinase, and compound B being an inhibitor of an anti-apoptotic protein of the Bcl-2 family. Another aspect of the present invention relates to the use of such combinations as described supra for the preparation of a medicament for the treatment or prophylaxis of a disease, particularly for the treatment of cancer. Another aspect of the present invention relates to the use of an anti- apoptotic protein from the Bcl-2 family as a sensitizer of cells to Mps-1 inhibitors. Another aspect of the present invention relates to the use of the ratio of pro-apoptotic and anti-apoptotic proteins from the Bcl-2 family in a biological sample as a biomarker for a Mps-1 kinase inhibitor treatment.

# Combinations for the treatment of cancer

The present invention relates to combinations of at least two compounds A and B, compound A being an inhibitor of Mps-1 kinase, and compound B being an inhibitor of an anti-apoptotic protein of the Bcl-2 family.

Another aspect of the present invention relates to the use of such combinations as described *supra* for the preparation of a medicament for the treatment or prophylaxis of a disease, particurlarly for the treatment of cancer. Another aspect of the present invention relates to the use of an anti-apoptotic protein from the Bcl-2 family as a sensitizer of cells to Mps-1 inhibitors.

Further, the present invention relates to a kit comprising a combination of:

- one or more compounds A, as defined *supra*, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;
- one or more compounds B, as defined *supra*, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and
- one or more pharmaceutical agents C;

in which optionally either or both of said compounds A and B are in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially.

The components may be administered independnently of one another by the oral, intravenous, topical, local installations, intraperitoneal or nasal route.

Another aspect of the present invention relates to the use of the ratio of pro-apoptotic and anti-apoptotic proteins from the Bcl-2 family in a biological sample as a biomarker for a Mps-1 kinase inhibitor treatment.

## BACKGROUND OF THE INVENTION

One component of the combinations of the present invention is a compound A which is an inhibitor of Mps-1 (Monopolar Spindle 1) kinase (also known as Tyrosine Threonine Kinase, TTK). Mps-1 is a dual specificity Ser/Thr kinase which plays a key role in the activation of the mitotic checkpoint (also known as spindle checkpoint, spindle assembly checkpoint, SAC) thereby ensuring proper chromosome segregation during mitosis [Abrieu A *et al.*, Cell, 2001, 106, 83-93]. Every dividing cell has to ensure equal separation of the replicated chromosomes into the two daughter cells. Upon entry into mitosis, chromosomes are attached at their kinetochores to the microtubules of the spindle apparatus. The mitotic checkpoint is a surveillance mechanism that is active as long as unattached kinetochores are present and prevents mitotic cells from entering anaphase and thereby completing cell division with unattached chromosomes [Suijkerbuijk SJ and Kops GJ, Biochemica et Biophysica Acta, 2008, 1786, 24-31; Musacchio A and Salmon ED, Nat Rev Mol Cell Biol., 2007, 8, 379-93]. Once all kinetochores are attached in a correct amphitelic, *i.e.* bipolar, fashion with the mitotic spindle, the checkpoint is satisfied and the cell enters anaphase and proceeds through mitosis. The mitotic checkpoint consists of a complex network of a number of essential proteins, including members of the MAD (mitotic arrest deficient, MAD 1-3) and Bub (Budding uninhibited by benzimidazole, Bub 1-3) families, the motor protein CENP-E, Mps-1 kinase as well as other components, many of these being over-expressed in proliferating cells (*e.g.* cancer cells) and tissues [Yuan B *et al.*, Clinical Cancer Research, 2006, 12, 405-10]. The essential role of Mps-1 kinase activity in mitotic checkpoint signalling has been shown by shRNA-silencing, chemical genetics as well as chemical inhibitors of Mps-1 kinase [Jelluma N *et al.*, PLos ONE, 2008, 3, e2415; Jones MH *et al.*, Current Biology, 2005, 15, 160-65; Dorer RK *et al.*, Current Biology, 2005, 15, 1070-76; Schmidt M *et al.*, EMBO Reports, 2005, 6, 866-72].

There is ample evidence linking reduced but incomplete mitotic checkpoint function with aneuploidy and tumorigenesis [Weaver BA and Cleveland DW, Cancer Research, 2007, 67, 10103-5; King RW, Biochimica et Biophysica Acta, 2008, 1786, 4-14]. In contrast, complete inhibition of the mitotic checkpoint has been recognised to result in severe chromosome missegregation and induction of apoptosis in tumour cells [Kops GJ *et al.*, Nature Reviews Cancer, 2005, 5, 773-85; Schmidt M and Medema RH, Cell Cycle, 2006, 5, 159-63; Schmidt M and Bastians H, Drug Resistance Updates, 2007, 10, 162-81].

Therefore, mitotic checkpoint abrogation through pharmacological inhibition of Mps-1 kinase or other components of the mitotic checkpoint represents a new approach for the treatment of proliferative disorders including solid tumours such as carcinomas and sarcomas and leukaemias and lymphoid malignancies or other disorders associated with uncontrolled cellular proliferation.

Established anti mitotic drugs such as vinca alkaloids, taxanes or epothilones activate the SAC inducing a mitotic arrest either by stabilising or destabilising microtubule dynamics. This arrest prevents separation of sister chromatids to form the two daughter cells. Prolonged arrest in mitosis forces a cell either into mitotic exit without cytokinesis or into mitotic catastrophe leading to cell death.

In contrast, inhibitors of Mps-1 induce a SAC inactivation that accelerates progression of cells through mitosis resulting in severe chromosomal missegregation and finally in cell death.

These findings suggest that Mps-1 inhibitors should be of therapeutic value for the treatment of proliferative disorders associated with enhanced uncontrolled proliferative cellular processes such as, for example, cancer, inflammation, arthritis, viral diseases, neurodegenerative diseases such as

Alzheimer's disease, cardiovascular diseases, or fungal diseases in a warm blooded animal such as man.

Therefore, inhibitors of Mps-1 represent valuable compounds that should complement therapeutic options either as single agents or in combination with other drugs.

Different compounds have been disclosed in prior art which show an inhibitory effect on Mps-1 kinase:

WO2010/124826A1 discloses substituted imidazoquinoxaline compounds as inhibitors of Mps-1 kinase or TTK. WO2011/026579A1 discloses substituted aminoquinoxalines as Mps-1 inhibitors. WO2011/063908A1, WO2011/064328A1 as well as WO2011/063907 A1 disclose triazolopyridine derivates as inhibitors of Mps-1 kinase.

Preferred compounds for the inhibition of Mps-1 in a combination according to the present invention are the substituted imidazopyridazine compounds of formula (I) as defined hereinafter.

Imidazopyridazine derivates have been disclosed for the treatment or prophylaxis of different diseases:

WO 2007/038314 A2 relates to fused heterocyclic compounds useful as kinase modulators, including MK2 modulation. In particular, WO 2007/038314 A2 relates to imidazo[1,2-b]pyridazines.

US patent application publication US 2008/0045536 A1 similarly relates to fused heterocyclic compounds useful as kinase modulators, including MK2 modulation. In particular, it relates to imidazo[1,2-b]pyridazines.

WO 2010/042699 A1 relates to fused heterocyclic compounds useful as kinase modulators, particularly CK2 modulation. In particular, WO 2010/042699 A1

relates to imidazo[1,2-b]pyridazines which are substituted with a nitrile group in position 3.

WO 2007/025090 A2 relates to heterocyclic compounds useful as inhibitors of MEK kinase. In particular, WO 2007/025090 A2 relates *inter alia* to imidazo[1,2-b]pyridazines.

WO 1998/08847 A1 relates to heterocyclic compounds useful as corticotropin releasing factor (hormone) CRF (CRH) antagonists. In particular, WO 1998/08847 A1 relates inter alia to imidazo[1,2-b]pyridazines.

WO 2011/013729A1 discloses fused imidazole derivatives as Mps-1 inhibitors.

WO 2012/032031A1 discloses imidazo[1,2-b]pyridazines as Mps-1 inhibitors.

Another component of the combinations of the present invention is a compound B which is an inhibitor of an anti-apoptotic protein of the Bcl-2 family. Bcl-2 (B-cell lymphoma 2) is the founding member of the Bcl-2 family of apoptosis regulator proteins encoded by the BCL2 gene (Bakhashi et al., Cell 1985, 41, 899ff; Cleary et al., Proc. Nat'l. Acad. Sci. USA, 1985, 82, 7439ff).

The Bcl-2 family is defined by the presence of up to four conserved "Bcl-2 homology" (BH) domains designated BH1, BH2, BH3, and BH4, all of which include α-helical segments (Chittenden et al., EMBO 1995, 14, 5589ff; Wang et al. Genes Dev. 1996, 10, 2859ff). Anti-apoptotic proteins, such as Bcl-2, Bcl-$X_L$, and Mcl-1, display sequence conservation in all BH domains. Pro-apoptotic proteins are divided into "multidomain" members (e.g. BAK, BAX), which possess homology in the BH1, BH2, and BH3 domains, and the "BH3-domain only" members (e.g. BID, BAD, BIM, BIK, NOXA, PUMA), that contain sequence homology exclusively in the BH3 amphipathic α-helical segment. BCL-2 family

members have the capacity to form homo- and heterodimers, suggesting that competitive binding and the ratio between pro- and anti-apoptotic protein levels dictates susceptibility to death stimuli. Anti-apoptotic proteins function to protect cells from pro-apoptotic excess, i.e., excessive programmed cell death. Additional "security" measures include regulating transcription of pro-apoptotic proteins and maintaining them as inactive conformers, requiring either proteolytic activation, dephosphorylation, or ligand-induced conformational change to activate pro-death functions.

In certain cell types, death signals received at the plasma membrane trigger apoptosis via a mitochondrial pathway (US8198405 B2). The mitochondria can serve as a gatekeeper of cell death by sequestering cytochrome c, a critical component of a cytosolic complex which activates caspase 9, leading to fatal downstream proteolytic events. Multidomain proteins such as Bcl-2/Bcl-$X_L$ and BAK/BAX play dueling roles of guardian and executioner at the mitochondrial membrane, with their activities further regulated by upstream BH3-only members of the Bcl-2 family. For example, BID is a member of the "BH3-domain only" subset of pro-apoptotic proteins, and transmits death signals received at the plasma membrane to effector pro-apoptotic proteins at the mitochondrial membrane. BID has the unique capability of interacting with both pro- and anti-apoptotic proteins, and upon activation by caspase 8, triggers cytochrome c release and mitochondrial apoptosis. Deletion and mutagenesis studies determined that the amphipathic α-helical BH3 segment of pro-apoptotic family members functions as a death domain and thus represents a critical structural motif for interacting with multidomain apoptotic proteins. Structural studies have demonstrated that the BH3 helix interacts with anti-apoptotic proteins by inserting into a hydrophobic groove formed by the interface of BH1, 2 and 3 domains. Activated BID can be bound and sequested by anti-apoptotic proteins (e.g., Bcl-2 and Bcl-$X_L$) and can trigger activation of the pro-apoptotic proteins BAX and BAK, leading to cytochrome c release and a mitochondrial apoptosis program.

Inhibitors of anti-apoptotic Bcl-2 proteins have been disclosed in prior art (e.g. US 8,188,077 B2).

However, the state of the art neither discloses the combinations of the present invention comprising an inhibitor of Mps-1 kinase and an inhibitor of an anti-apoptotic protein of the Bcl-2 family nor the use of an anti-apoptotic protein from the Bcl-2 family as a sensitizer of cells to Mps-1 inhibitors.

**SUMMARY of the INVENTION**

Surprisingly it was observed that the depletion or pharmacological inhibition of an anti-apoptotic protein of the Bcl-2 family sensitized tumor cells to Mps-1 inhibitors.

Therefore, in accordance with a first aspect, the present invention covers combinations of at least two compounds A and B, compound A being an inhibitor of Mps-1 kinase, and compound B being an inhibitor of an anti-apoptotic protein of the Bcl-2 family.

The combinations of at least two compounds A and B, as decribed and defined herein, are also referred to as "combinations of the present invention"; a compound A, as decribed and defined herein, is also referred to as "compound A of the the present invention" and a compound B, as decribed and defined herein, is also referred to as "compound B of the the present invention", respectively. Compounds A and B jointly are also referred to as "compounds of the present invention".

Further, the present invention relates to :

a kit comprising :

- a combination of :

component A : one or more Mps-1 kinase inhibitors, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

component B : one or more inhibitors of an anti-apoptotic protein from the Bcl-2 family, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and, optionally,

component C : one or more further pharmaceutical agents ;

in which optionally either or both of said components A and B in any of the above-mentioned combinations are in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially. The components may be administered independnently of one another by the oral, intravenous, topical, local installations, intraperitoneal or nasal route.

In accordance with another aspect, the present invention covers the combinations as described *supra* for the treatment or prophylaxis of a disease.

In accordance with another aspect, the present invention covers the use of such combinations as described *supra* for the preparation of a medicament for the treatment or prophylaxis of of a disease.

In accordance with another aspect, the present invention covers an anti-apoptotic protein from the Bcl-2 family for the use as a sensitizer of cells to Mps-1 inhibitors.

In accordance with another aspect, the present invention covers the use of an anti-apoptotic protein from the Bcl-2 family as a sensitizer of cells to Mps-1 inhibitors.

Further, the present invention relates to the use of the ratio of pro-apoptotic and anti-apoptotic proteins from the Bcl-2 family in a biological sample as a biomarker for a Mps-1 kinase inhibitor treatment.

## DETAILLED DESCRIPTION of the INVENTION

The terms as mentioned in the present text have preferably the following meanings :

The term "halogen atom" or "halo-" is to be understood as meaning a fluorine, chlorine, bromine or iodine atom.

The term "$C_1$-$C_6$-alkyl" is to be understood as preferably meaning a linear or branched, saturated, monovalent hydrocarbon group having 1, 2, 3, 4, 5 or 6 carbon atoms, *e.g.* a methyl, ethyl, propyl, butyl, pentyl, hexyl, iso-propyl, iso-butyl, sec-butyl, tert-butyl, iso-pentyl, 2-methylbutyl, 1-methylbutyl, 1-ethylpropyl, 1,2-dimethylpropyl, neo-pentyl, 1,1-dimethylpropyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 2-ethylbutyl, 1-ethylbutyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 2,3-dimethylbutyl, 1,3-dimethylbutyl, or 1,2-dimethylbutyl group, or an isomer thereof. Particularly, said group has 1, 2, 3 or 4 carbon atoms ("$C_1$-$C_4$-alkyl"), *e.g.* a methyl, ethyl, propyl, butyl, iso-propyl, iso-butyl, sec-butyl, tert-butyl group, more particularly 1, 2 or 3 carbon atoms ("$C_1$-$C_3$-alkyl"), *e.g.* a methyl, ethyl, n-propyl- or iso-propyl group.

The term "halo-$C_1$-$C_6$-alkyl" is to be understood as preferably meaning a linear or branched, saturated, monovalent hydrocarbon group in which the term "$C_1$-$C_6$-alkyl" is defined *supra*, and in which one or more of the hydrogen atoms is replaced, in identically or differently, by a halogen atom. Particularly, said halogen atom is F. Said halo-$C_1$-$C_6$-alkyl group is, for example, -$CF_3$, -$CHF_2$, -$CH_2F$, -$CF_2CF_3$, or -$CH_2CF_3$.

The term "$C_1$-$C_6$-alkoxy" is to be understood as preferably meaning a linear or branched, saturated, monovalent group of formula -O-($C_1$-$C_6$-alkyl), in which the term "$C_1$-$C_6$-alkyl" is defined *supra*, *e.g.* a methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, tert-butoxy, sec-butoxy, pentoxy, iso-pentoxy, or n-hexoxy group, or an isomer thereof.

The term "halo-$C_1$-$C_6$-alkoxy" is to be understood as preferably meaning a linear or branched, saturated, monovalent $C_1$-$C_6$-alkoxy group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, in identically or differently, by a halogen atom. Particularly, said halogen atom is F. Said halo-$C_1$-$C_6$-alkoxy group is, for example, -$OCF_3$, -$OCHF_2$, -$OCH_2F$, -$OCF_2CF_3$, or -$OCH_2CF_3$.

The term "$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl" is to be understood as preferably meaning a linear or branched, saturated, monovalent $C_1$-$C_6$-alkyl group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, in identically or differently, by a $C_1$-$C_6$-alkoxy group, as defined *supra*, *e.g.* methoxyalkyl, ethoxyalkyl, propyloxyalkyl, iso-propoxyalkyl, butoxyalkyl, iso-butoxyalkyl, tert-butoxyalkyl, sec-butoxyalkyl, pentyloxyalkyl, iso-pentyloxyalkyl, hexyloxyalkyl group, or an isomer thereof.

The term "halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl" is to be understood as preferably meaning a linear or branched, saturated, monovalent $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl group, as defined *supra*, in which one or more of the hydrogen atoms is

replaced, in identically or differently, by a halogen atom. Particularly, said halogen atom is F. Said halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl group is, for example, $-CH_2CH_2OCF_3$, $-CH_2CH_2OCHF_2$, $-CH_2CH_2OCH_2F$, $-CH_2CH_2OCF_2CF_3$, or $-CH_2CH_2OCH_2CF_3$.

The term "$C_2$-$C_6$-alkenyl" is to be understood as preferably meaning a linear or branched, monovalent hydrocarbon group, which contains one or more double bonds, and which has 2, 3, 4, 5 or 6 carbon atoms, particularly 2 or 3 carbon atoms ("$C_2$-$C_3$-alkenyl"), it being understood that in the case in which said alkenyl group contains more than one double bond, then said double bonds may be isolated from, or conjugated with, each other. Said alkenyl group is, for example, a vinyl, allyl, (E)-2-methylvinyl, (Z)-2-methylvinyl, homoallyl, (E)-but-2-enyl, (Z)-but-2-enyl, (E)-but-1-enyl, (Z)-but-1-enyl, pent-4-enyl, (E)-pent-3-enyl, (Z)-pent-3-enyl, (E)-pent-2-enyl, (Z)-pent-2-enyl, (E)-pent-1-enyl, (Z)-pent-1-enyl, hex-5-enyl, (E)-hex-4-enyl, (Z)-hex-4-enyl, (E)-hex-3-enyl, (Z)-hex-3-enyl, (E)-hex-2-enyl, (Z)-hex-2-enyl, (E)-hex-1-enyl, (Z)-hex-1-enyl, isopropenyl, 2-methylprop-2-enyl, 1-methylprop-2-enyl, 2-methylprop-1-enyl, (E)-1-methylprop-1-enyl, (Z)-1-methylprop-1-enyl, 3-methylbut-3-enyl, 2-methylbut-3-enyl, 1-methylbut-3-enyl, 3-methylbut-2-enyl, (E)-2-methylbut-2-enyl, (Z)-2-methylbut-2-enyl, (E)-1-methylbut-2-enyl, (Z)-1-methylbut-2-enyl, (E)-3-methylbut-1-enyl, (Z)-3-methylbut-1-enyl, (E)-2-methylbut-1-enyl, (Z)-2-methylbut-1-enyl, (E)-1-methylbut-1-enyl, (Z)-1-methylbut-1-enyl, 1,1-dimethylprop-2-enyl, 1-ethylprop-1-enyl, 1-propylvinyl, 1-isopropylvinyl, 4-methylpent-4-enyl, 3-methylpent-4-enyl, 2-methylpent-4-enyl, 1-methylpent-4-enyl, 4-methylpent-3-enyl, (E)-3-methylpent-3-enyl, (Z)-3-methylpent-3-enyl, (E)-2-methylpent-3-enyl, (Z)-2-methylpent-3-enyl, (E)-1-methylpent-3-enyl, (Z)-1-methylpent-3-enyl, (E)-4-methylpent-2-enyl, (Z)-4-methylpent-2-enyl, (E)-3-methylpent-2-enyl, (Z)-3-methylpent-2-enyl, (E)-2-methylpent-2-enyl, (Z)-2-methylpent-2-enyl, (E)-1-methylpent-2-enyl, (Z)-1-methylpent-2-enyl, (E)-4-methylpent-1-enyl, (Z)-4-methylpent-1-enyl, (E)-3-methylpent-1-enyl, (Z)-3-methylpent-1-enyl, (E)-2-methylpent-1-enyl, (Z)-2-methylpent-1-

enyl, (E)-1-methylpent-1-enyl, (Z)-1-methylpent-1-enyl, 3-ethylbut-3-enyl, 2-ethylbut-3-enyl, 1-ethylbut-3-enyl, (E)-3-ethylbut-2-enyl, (Z)-3-ethylbut-2-enyl, (E)-2-ethylbut-2-enyl, (Z)-2-ethylbut-2-enyl, (E)-1-ethylbut-2-enyl, (Z)-1-ethylbut-2-enyl, (E)-3-ethylbut-1-enyl, (Z)-3-ethylbut-1-enyl, 2-ethylbut-1-enyl, (E)-1-ethylbut-1-enyl, (Z)-1-ethylbut-1-enyl, 2-propylprop-2-enyl, 1-propylprop-2-enyl, 2-isopropylprop-2-enyl, 1-isopropylprop-2-enyl, (E)-2-propylprop-1-enyl, (Z)-2-propylprop-1-enyl, (E)-1-propylprop-1-enyl, (Z)-1-propylprop-1-enyl, (E)-2-isopropylprop-1-enyl, (Z)-2-isopropylprop-1-enyl, (E)-1-isopropylprop-1-enyl, (Z)-1-isopropylprop-1-enyl, (E)-3,3-dimethylprop-1-enyl, (Z)-3,3-dimethylprop-1-enyl, 1-(1,1-dimethylethyl)ethenyl, buta-1,3-dienyl, penta-1,4-dienyl, hexa-1,5-dienyl, or methylhexadienyl group. Particularly, said group is vinyl or allyl.

The term "$C_2$-$C_6$-alkynyl" is to be understood as preferably meaning a linear or branched, monovalent hydrocarbon group which contains one or more triple bonds, and which contains 2, 3, 4, 5 or 6 carbon atoms, particularly 2 or 3 carbon atoms ("$C_2$-$C_3$-alkynyl"). Said $C_2$-$C_6$-alkynyl group is, for example, ethynyl, prop-1-ynyl, prop-2-ynyl, but-1-ynyl, but-2-ynyl, but-3-ynyl, pent-1-ynyl, pent-2-ynyl, pent-3-ynyl, pent-4-ynyl, hex-1-ynyl, hex-2-inyl, hex-3-inyl, hex-4-ynyl, hex-5-ynyl, 1-methylprop-2-ynyl, 2-methylbut-3-ynyl, 1-methylbut-3-ynyl, 1-methylbut-2-ynyl, 3-methylbut-1-ynyl, 1-ethylprop-2-ynyl, 3-methylpent-4-ynyl, 2-methylpent-4-ynyl, 1-methylpent-4-ynyl, 2-methylpent-3-ynyl, 1-methylpent-3-ynyl, 4-methylpent-2-ynyl, 1-methylpent-2-ynyl, 4-methylpent-1-ynyl, 3-methylpent-1-ynyl, 2-ethylbut-3-ynyl, 1-ethylbut-3-ynyl, 1-ethylbut-2-ynyl, 1-propylprop-2-ynyl, 1-isopropylprop-2-ynyl, 2,2-dimethylbut-3-inyl, 1,1-dimethylbut-3-ynyl, 1,1-dimethylbut-2-ynyl, or 3,3-dimethylbut-1-ynyl group. Particularly, said alkynyl group is ethynyl, prop-1-ynyl, or prop-2-inyl.

The term "$C_3$-$C_6$-cycloalkyl" is to be understood as preferably meaning a saturated, monovalent, mono-, or bicyclic hydrocarbon ring which contains 3,

4, 5 or 6 carbon atoms. Said $C_3$-$C_6$-cycloalkyl group is for example, a monocyclic hydrocarbon ring, *e.g.* a cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl or a bicyclic hydrocarbon ring. Said cycloalkyl ring can optionally contain one or more double bonds *e.g.* cycloalkenyl, such as a cyclopropenyl, cyclobutenyl, cyclopentenyl or cyclohexenyl group, wherein the bond between said ring with the rest of the molecule may be to any carbon atom of said ring, be it saturated or unsaturated.

The term "heterocyclic ring", as used in the term "4-, 5- or 6- membered heterocyclic ring", or "4- to 6-membered heterocyclic ring" or "4- to 5-membered heterocyclic ring", for example, as used in the definition of compounds of general formula (I) as defined herein, is to be understood as meaning a saturated or partially unsaturated, monocyclic nitrogen atom-containing ring, said nitrogen atom being the point of attachment of said heterocyclic ring with the rest of the molecule. Said nitrogen atom-containing ring optionally further contains 1 or 2 heteroatom-containing groups selected from O and C(=O). Particularly, without being limited thereto, said nitrogen atom-containing ring can be a 4-membered ring, such as an azetidinyl ring, for example, or a 5-membered ring, such as a pyrrolidinyl ring or oxazolidinonyl ring, for example, or a 6-membered ring, such as a piperidinyl or morpholinyl ring, for example ; it being reiterated that any of the above-mentioned nitrogen atom-containing rings can further contain 1 or 2 heteroatom-containing groups selected from O and C(=O).
As mentioned *supra*, said nitrogen atom-containing ring can be partially unsaturated, *i.e.* it can contain one or more double bonds, such as, without being limited thereto, a 2,5-dihydro-1H-pyrrolyl ring, for example.

The term "3- to 10-membered heterocycloalkyl" is to be understood as preferably meaning a saturated or partially unsaturated, monovalent, mono- or bicyclic hydrocarbon ring which contains 2, 3, 4, 5, 6, 7, 8, or 9 carbon atoms, and one or more heteroatom-containing groups selected from C(=O),

O, S, S(=O), $S(=O)_2$, NH, NR'', wherein R'' represents a $C_1$-$C_6$-alkyl, $C_3$-$C_6$-cycloalkyl, -C(=O)-($C_1$-$C_6$-alkyl) or -C(=O)-($C_1$-$C_6$-cycloalkyl). Particularly, said ring can contain 2, 3, 4, or 5 carbon atoms, and one or more of the above-mentioned heteroatom-containing groups (a "3- to 6-membered heterocycloalkyl"), more particularly said ring can contain 4 or 5 carbon atoms, and one or more of the above-mentioned heteroatom-containing groups (a "5- to 6-membered heterocycloalkyl"). Said heterocycloalkyl ring is for example, a monocyclic heterocycloalkyl ring such as an oxyranyl, oxetanyl, aziridinyl, azetidinyl, tetrahydrofuranyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, pyrrolinyl, tetrahydropyranyl, piperidinyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, trithianyl, or chinuclidinyl group. Optionally, said heterocycloalkyl ring can contain one or more double bonds, *e.g.* 4H-pyranyl, 2H-pyranyl, 3H-diazirinyl, 2,5-dihydro-1H-pyrrolyl, [1,3]dioxolyl, 4H-[1,3,4]thiadiazinyl, 2,5-dihydrofuranyl, 2,3-dihydrofuranyl, 2,5-dihydrothiophenyl, 2,3-dihydrothiophenyl, 4,5-dihydro-1,3-oxazolyl, 4,4-dimethyl-4,5-dihydro-1,3-oxazolyl , or 4H-[1,4]thiazinyl group, or, it may be benzo fused.

The term "aryl" is to be understood as preferably meaning a monovalent, aromatic or partially aromatic, mono-, or bi- or tricyclic hydrocarbon ring having 6, 7, 8, 9, 10, 11, 12, 13 or 14 carbon atoms (a "$C_6$-$C_{14}$-aryl" group), particularly a ring having 6 carbon atoms (a "$C_6$-aryl" group), *e.g.* a phenyl group, or a biphenyl group, or a ring having 9 carbon atoms (a "$C_9$-aryl" group), *e.g.* an indanyl or indenyl group, or a ring having 10 carbon atoms (a "$C_{10}$-aryl" group), *e.g.* a tetralinyl, dihydronaphthyl, or naphthyl group, or a ring having 13 carbon atoms, (a "$C_{13}$-aryl" group), *e.g.* a fluorenyl group, or a ring having 14 carbon atoms, (a "$C_{14}$-aryl" group), *e.g.* an anthranyl group.

The term "heteroaryl" is understood as preferably meaning a monovalent, aromatic, mono- or bicyclic aromatic ring system having 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 ring atoms (a "5- to 14-membered heteroaryl" group), particularly

5 or 6 or 9 or 10 atoms, and which contains at least one heteroatom which may be identical or different, said heteroatom being such as oxygen, nitrogen or sulfur, and can be monocyclic, bicyclic, or tricyclic, and in addition in each case can be benzocondensed. Particularly, heteroaryl is selected from thienyl, furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, thia-4H-pyrazolyl *etc.*, and benzo derivatives thereof, such as, for example, benzofuranyl, benzothienyl, benzoxazolyl, benzisoxazolyl, benzimidazolyl, benzotriazolyl, indazolyl, indolyl, isoindolyl, *etc.*; or pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, *etc.*, and benzo derivatives thereof, such as, for example, quinolinyl, quinazolinyl, isoquinolinyl, *etc.*; or azocinyl, indolizinyl, purinyl, *etc.*, and benzo derivatives thereof; or cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthpyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, xanthenyl, or oxepinyl, *etc.* More particularly, heteroaryl is selected from pyridyl, benzofuranyl, benzisoxazolyl, indazolyl, quinazolinyl, thienyl, quinolinyl, benzothienyl, pyrazolyl, or furanyl.

The term "alkylene" is understood as preferably meaning an optionally substituted hydrocarbon chain (or "tether") having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms, *i.e.* an optionally substituted $-CH_2-$ ("methylene" or "single membered tether" or, for example $-C(CH_3)_2-$), $-CH_2-CH_2-$ ("ethylene", "dimethylene", or "two-membered tether", for example $-C(CH_3)_2-C(CH_3)_2-$), $-CH_2-CH_2-CH_2-$ ("propylene", "trimethylene", or "three-membered tether", for example $-CH_2-C(H)(CH_3)-CH_2-$, $-CH_2-C(CH_3)_2-CH_2-$), $-CH_2-CH_2-CH_2-CH_2-$ ("butylene", "tetramethylene", or "four-membered tether"), $-CH_2-CH_2-CH_2-CH_2-CH_2-$ ("pentylene", "pentamethylene" or "five-membered ether"), or $-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-$ ("hexylene", "hexamethylene", or six-membered tether") group. Particularly, said alkylene tether has 1, 2, 3, 4, or 5 carbon atoms, more particularly 1 or 2 carbon atoms.

The term "$C_1$-$C_6$", as used throughout this text, *e.g.* in the context of the definition of "$C_1$-$C_6$-alkyl", "$C_1$-$C_6$-haloalkyl", "$C_1$-$C_6$-alkoxy", or "$C_1$-$C_6$-haloalkoxy" is to be understood as meaning an alkyl group having a finite number of carbon atoms of 1 to 6, *i.e.* 1, 2, 3, 4, 5, or 6 carbon atoms. It is to be understood further that said term "$C_1$-$C_6$" is to be interpreted as any sub-range comprised therein, *e.g.* $C_1$-$C_6$, $C_2$-$C_5$, $C_3$-$C_4$, $C_1$-$C_2$, $C_1$-$C_3$, $C_1$-$C_4$, $C_1$-$C_5$, $C_1$-$C_6$; particularly $C_1$-$C_2$, $C_1$-$C_3$, $C_1$-$C_4$, $C_1$-$C_5$, $C_1$-$C_6$; more particularly $C_1$-$C_4$; in the case of "$C_1$-$C_6$-haloalkyl" or "$C_1$-$C_6$-haloalkoxy" even more particularly $C_1$-$C_2$.

Similarly, as used herein, the term "$C_2$-$C_6$", as used throughout this text, *e.g.* in the context of the definitions of "$C_2$-$C_6$-alkenyl" and "$C_2$-$C_6$-alkynyl", is to be understood as meaning an alkenyl group or an alkynyl group having a finite number of carbon atoms of 2 to 6, *i.e.* 2, 3, 4, 5, or 6 carbon atoms. It is to be understood further that said term "$C_2$-$C_6$" is to be interpreted as any sub-range comprised therein, *e.g.* $C_2$-$C_6$, $C_3$-$C_5$, $C_3$-$C_4$, $C_2$-$C_3$, $C_2$-$C_4$, $C_2$-$C_5$; particularly $C_2$-$C_3$.

Further, as used herein, the term "$C_3$-$C_6$", as used throughout this text, *e.g.* in the context of the definition of "$C_3$-$C_6$-cycloalkyl", is to be understood as meaning a cycloalkyl group having a finite number of carbon atoms of 3 to 6, *i.e.* 3, 4, 5 or 6 carbon atoms. It is to be understood further that said term "$C_3$-$C_6$" is to be interpreted as any sub-range comprised therein, *e.g.* $C_3$-$C_6$, $C_4$-$C_5$, $C_3$-$C_5$, $C_3$-$C_4$, $C_4$-$C_6$, $C_5$-$C_6$; particularly $C_3$-$C_6$.

As used herein, the term "leaving group" refers to an atom or a group of atoms that is displaced in a chemical reaction as stable species taking with it the bonding electrons. Preferably, a leaving group is selected from the group comprising: halo, in particular chloro, bromo or iodo, methanesulfonyloxy, p-toluenesulfonyloxy, trifluoromethanesulfonyloxy, nonafluorobutanesulfonyloxy, (4-bromo-benzene)sulfonyloxy, (4-nitro-

benzene)sulfonyloxy, (2-nitro-benzene)-sulfonyloxy, (4-isopropyl-benzene)sulfonyloxy, (2,4,6-tri-isopropyl-benzene)-sulfonyloxy, (2,4,6-trimethyl-benzene)sulfonyloxy, (4-tertbutyl-benzene)sulfonyloxy, benzenesulfonyloxy, and (4-methoxy-benzene)sulfonyloxy.

As used herein, the term "one or more times", *e.g.* in the definition of the substituents of the compounds of the general formulae of the present invention, is understood as meaning "one, two, three, four or five times, particularly one, two, three or four times, more particularly one, two or three times, even more particularly one or two times".

Where the plural form of the word compounds, salts, polymorphs, hydrates, solvates and the like, is used herein, this is taken to mean also a single compound, salt, polymorph, isomer, hydrate, solvate or the like.

The compounds of this invention contain one or more asymmetric centre, depending upon the location and nature of the various substituents desired. Asymmetric carbon atoms may be present in the (R) or (S) configuration. In certain instances, asymmetry may also be present due to restricted rotation about a given bond, for example, the central bond adjoining two substituted aromatic rings of the specified compounds.

Substituents on a ring may also be present in either cis or trans form. It is intended that all such configurations are included within the scope of the present invention.

Preferred compounds are those which produce the more desirable biological activity. Separated, pure or partially purified isomers and stereoisomers or racemic or diastereomeric mixtures of the compounds of this invention are also included within the scope of the present invention. The purification and the separation of such materials can be accomplished by standard techniques known in the art.

The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example, by the formation of diastereoisomeric salts using an optically active acid or base or formation of covalent diastereomers. Examples of appropriate acids are tartaric, diacetyltartaric, ditoluoyltartaric and camphorsulfonic acid. Mixtures of diastereoisomers can be separated into their individual diastereomers on the basis of their physical and/or chemical differences by methods known in the art, for example, by chromatography or fractional crystallisation. The optically active bases or acids are then liberated from the separated diastereomeric salts. A different process for separation of optical isomers involves the use of chiral chromatography (*e.g.*, chiral HPLC columns), with or without conventional derivatisation, optimally chosen to maximise the separation of the enantiomers. Suitable chiral HPLC columns are manufactured by Diacel, *e.g.*, Chiracel OD and Chiracel OJ among many others, all routinely selectable. Enzymatic separations, with or without derivatisation, are also useful. The optically active compounds of this invention can likewise be obtained by chiral syntheses utilizing optically active starting materials.

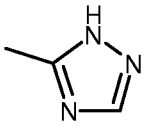
In order to limit different types of isomers from each other reference is made to IUPAC Rules Section E (Pure Appl Chem 45, 11-30, 1976).

The invention also includes all suitable isotopic variations of a compound of the invention. An isotopic variation of a compound of the invention is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually or predominantly found in nature. Examples of isotopes that can be incorporated into a compound of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulphur, fluorine, chlorine, bromine and iodine, such as $^{2}H$ (deuterium), $^{3}H$ (tritium), $^{11}C$, $^{13}C$, $^{14}C$, $^{15}N$, $^{17}O$, $^{18}O$, $^{32}P$, $^{33}P$, $^{33}S$, $^{34}S$, $^{35}S$, $^{36}S$, $^{18}F$, $^{36}Cl$, $^{82}Br$, $^{123}I$, $^{124}I$, $^{129}I$ and $^{131}I$, respectively. Certain isotopic

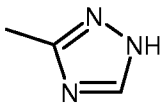
variations of a compound of the invention, for example, those in which one or more radioactive isotopes such as $^{3}H$ or $^{14}C$ are incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated and carbon-14, i.e., $^{14}C$, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of a compound of the invention can generally be prepared by conventional procedures known by a person skilled in the art such as by the illustrative methods or by the preparations described in the examples hereafter using appropriate isotopic variations of suitable reagents.

The present invention includes all possible stereoisomers of the compounds of the present invention as single stereoisomers, or as any mixture of said stereoisomers, in any ratio. Isolation of a single stereoisomer, *e.g.* a single enantiomer or a single diastereomer, of a compound of the present invention may be achieved by any suitable state of the art method, such as chromatography, especially chiral chromatography, for example.

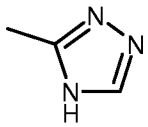
Further, the compounds of the present invention may exist as tautomers. For example, any compound of the present invention which contains a pyrazole moiety as a heteroaryl group for example can exist as a 1H tautomer, or a 2H tautomer, or even a mixture in any amount of the two tautomers, or a triazole moiety for example can exist as a 1H tautomer, a 2H tautomer, or a 4H tautomer, or even a mixture in any amount of said 1H, 2H and 4H tautomers, *viz.* :



1H-tautomer



2H-tautomer



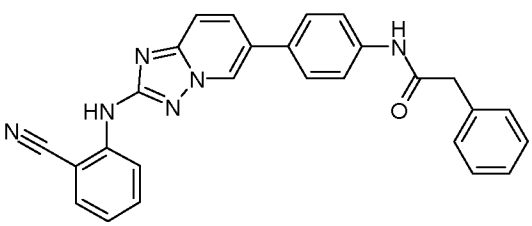
4H-tautomer.

The present invention includes all possible tautomers of the compounds of the present invention as single tautomers, or as any mixture of said tautomers, in any ratio.

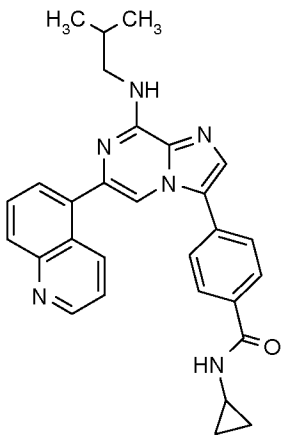
Furthermore, the present invention includes all possible crystalline forms, or polymorphs, of the compounds of the present invention, either as single polymorphs, or as a mixture of more than one polymorphs, in any ratio.

In accordance with a first aspect, the present invention relates to combinations of at least two compounds A and B, compound A being an inhibitor of Mps-1 kinase, and compound B being an inhibitor of an anti-apoptotic protein of the Bcl-2 family.

The synergistic behavior of a combination of the present invention is demonstrated herein with the structurally different Mps-1 inhibitors BAY 2 and BAY 3:



BAY 2

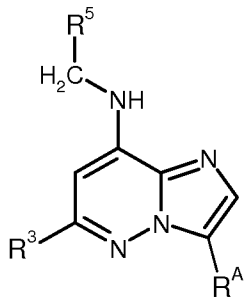


BAY 3

This makes it evident, that principially any Mps-1 inhibitor can be used in a combination of the present invention.

So, compound A can be selected from inhibitors of Mps-1 kinase specifically or generically disclosed e.g. in the following publications which are incorporated herein by reference:
WO2011/113862A, WO2011/151259A, WO2012/032031A, WO2011/063908A, WO2011/064328A, WO2011/063907A, WO2011/157688A, WO2012/080229A, WO2012/080228A, WO2012/080234A, WO2012/080230A, WO2012/080236A, WO2009/156315A, WO2012/013557A, WO2009/02482A, WO2010/111406A, WO2011/013729A1, WO2013/087579, WO2012/143329, WO2012/032031, Kenichi Kusakabe et al.: Diaminopyridine-Based Potent and Selective Mps1 Kinase Inhibitors Binding to an Unusual Flipped-Peptide Conformation, ACS Med. Chem. Lett. 2012, 3, 560−564;
or contained in the following patent applications which are incorporated herein by reference: EP13157453.5, PCT/EP2013/054841.

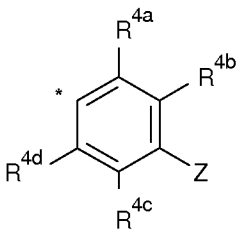
Preferably, the compound A being an inhibitor of Mps-1 kinase is selected from the group of compounds of general formula (I) :



(I)

in which :

$R^A$ represents a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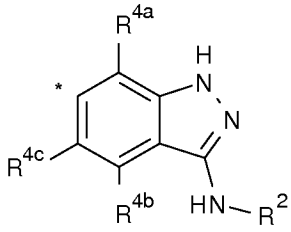
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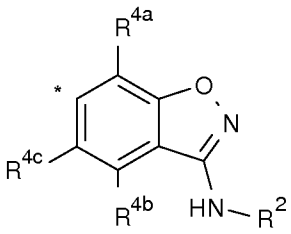
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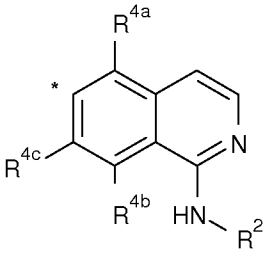
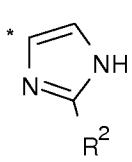

-group ;

wherein * indicates the point of attachment of said groups with the rest of the molecule ;

Z represents a -C(=O)N(H)$R^2$ or -C(=S)N(H)$R^2$ group, or a group selected from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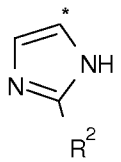
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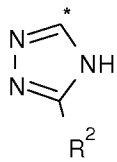
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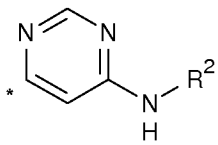
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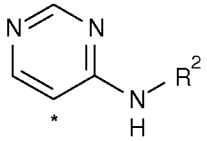
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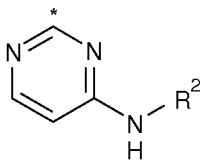
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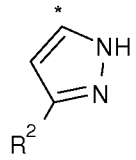
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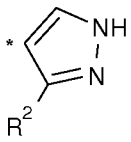
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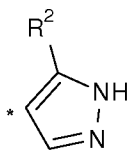
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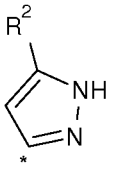
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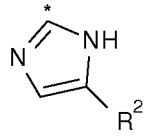

;

wherein * indicates the point of attachment of said groups with the rest of the molecule ;

$R^2$ represents a hydrogen atom, or a $C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})N$-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, -$C_1$-$C_6$-alkyl-CN, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, $C_2$-$C_6$-alkenyl-, $C_2$-$C_6$-alkynyl- or $C_3$-$C_6$-cycloalkyl- group ;
wherein said $C_3$-$C_6$-cycloalkyl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 groups selected from: halogen, -OH, -CN, $C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy-, halo-$C_1$-$C_6$-alkyl-;

$R^3$ represents a hydrogen atom or a halogen atom, or a -CN, $C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy-, -$(CH_2)_m$-$C_2$-$C_6$-alkenyl, -$(CH_2)_m$-$C_4$-$C_8$-cycloalkenyl, -$(CH_2)_m$-$C_2$-$C_6$-alkynyl, -$(CH_2)_m$-$C_3$-$C_6$-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-$C_1$-$C_6$-alkyl-, heteroaryl-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})N$-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, $C_3$-$C_6$-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, $C_2$-$C_6$-alkenyl-, $C_4$-$C_8$-cycloalkenyl-, $C_2$-$C_6$-alkynyl-, aryl-, -$C_1$-$C_6$-alkyl-aryl, -$C_1$-$C_6$-alkyl-heteroaryl, heteroaryl-, $C_1$-$C_6$-alkyl-X-, -X-$(CH_2)_m$-$C_2$-$C_6$-alkenyl, -X-$(CH_2)_m$-$C_4$-$C_8$-cycloalkenyl, -X-$(CH_2)_m$-$C_2$-$C_6$-alkynyl, -X-$(CH_2)_m$-$C_3$-$C_6$-cycloalkyl, -X-$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -X-$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-X-, heteroaryl-X-, -C(=O)$R^6$, -C(=O)N(H)$R^{6a}$, -C(=O)N($R^{6a}$)$R^{6b}$, -C(=O)O-$R^6$, -N($R^{6a}$)$R^{6b}$, -$NO_2$, -N(H)C(=O)$R^6$, -O$R^6$, -S$R^6$, -S(=O)$R^6$, -S(=O)$_2R^6$, -S(=O)(=N$R^{6a}$)$R^{6b}$, -S(=O)$_2$N($R^{6b}$)$R^{6c}$, -S-$(CH_2)_n$-N($R^{6a}$)$R^{6b}$ or -S-$(CH_2)_n$-(3- to 7-membered heterocycloalkyl) group ;
wherein said $C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy-, -$(CH_2)_m$-$C_2$-$C_6$-alkenyl, -$(CH_2)_m$-$C_2$-$C_6$-alkynyl, -$(CH_2)_m$-$C_3$-$C_6$-cycloalkyl, aryl-$C_1$-$C_6$-alkyl-, heteroaryl-$C_1$-$C_6$-alkyl-, $C_3$-$C_6$-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, $C_2$-$C_6$-alkenyl-, $C_4$-$C_8$-cycloalkenyl-, $C_2$-$C_6$-alkynyl-, aryl-, $C_1$-$C_6$-alkyl-X-, -X-$(CH_2)_m$-$C_2$-$C_6$-alkenyl,

-X-$(CH_2)_m$-$C_4$-$C_8$-cycloalkenyl, -X-$(CH_2)_m$-$C_2$-$C_6$-alkynyl, -X-$(CH_2)_m$-$C_3$-$C_6$-cycloalkyl, -X-$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -X-$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-X-, heteroaryl-X-, -$C_1$-$C_6$-alkyl-aryl, -$C_1$-$C_6$-alkyl-heteroaryl or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 $R^7$ groups ;

$R^{4a}$, $R^{4b}$, $R^{4c}$, $R^{4d}$

represent, independently from each other, a hydrogen or halogen atom, or a -CN, $C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})N$-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, -C(=O)$R^6$, -C(=O)N(H)$R^{6a}$, -C(=O)N($R^{6a}$)$R^{6b}$, -C(=O)O-$R^6$, -N($R^{6a}$)$R^{6b}$, -$NO_2$, -N(H)C(=O)$R^6$, -N($R^{6c}$)C(=O)$R^6$, -N(H)C(=O)N($R^{6a}$)$R^{6b}$, -N($R^{6c}$)C(=O)N($R^{6a}$)$R^{6b}$, -N(H)C(=O)O$R^6$, -N($R^{6c}$)C(=O)O$R^6$, -N(H)S(=O)$R^6$, -N($R^{6c}$)S(=O)$R^6$, -N(H)$S(=O)_2R^6$, -N($R^{6c}$)$S(=O)_2R^6$, -N=S(=O)($R^{6a}$)$R^{6b}$, -O$R^6$, -O(C=O)$R^6$, -O(C=O)N($R^{6a}$)$R^{6b}$, -O(C=O)O$R^6$, -S$R^6$, -S(=O)$R^6$, -S(=O)N(H)$R^6$, -S(=O)N($R^{6a}$)$R^{6b}$, -$S(=O)_2R^6$, -$S(=O)_2$N(H)$R^{6a}$, -$S(=O)_2$N($R^{6a}$)$R^{6b}$, -S(=O)(=N$R^{6c}$)$R^6$ group ;

$R^5$ represents a hydrogen atom, or a $C_1$-$C_6$-alkyl-, -$(CH_2)_n$-$C_2$-$C_6$-alkenyl, -$(CH_2)_n$-$C_2$-$C_6$-alkynyl, -$(CH_2)_m$-$C_3$-$C_6$-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-$C_1$-$C_6$-alkyl-, heteroaryl-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})N$-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, -$C_1$-$C_6$-alkyl-CN, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, $C_3$-$C_6$-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, $C_2$-$C_6$-alkenyl-, $C_4$-$C_8$-cycloalkenyl-, $C_2$-$C_6$-alkynyl-,aryl- or heteroaryl- group ;

wherein said $C_1$-$C_6$-alkyl-, -$(CH_2)_n$-$C_2$-$C_6$-alkenyl, -$(CH_2)_n$-$C_2$-$C_6$-alkynyl, -$(CH_2)_m$-$C_3$-$C_6$-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-$C_1$-$C_6$-alkyl-, heteroaryl-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})N$-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, -$C_1$-$C_6$-alkyl-CN,

$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, $C_3$-$C_6$-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, $C_4$-$C_8$-cycloalkenyl-, aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 $R^8$ groups ;

$R^6$, $R^{6a}$, $R^{6b}$, $R^{6c}$

represent, independently from each other, a hydrogen atom, or a $C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, $C_3$-$C_6$-cycloalkyl-, $C_2$-$C_6$-alkenyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, aryl-$C_1$-$C_6$-alkyl- or heteroaryl-$C_1$-$C_6$-alkyl- group ;

$R^7$ represents a hydrogen or halogen atom, or a HO-, -CN, $C_1$-$C_6$-alkoxy-, $C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})N$-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, $C_2$-$C_6$-alkenyl, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$ or $-S(=O)(=NR^{6c})R^6$ group ;

wherein said $C_1$-$C_6$-alkoxy-, aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2 or 3 $C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy-, halo-$C_1$-$C_6$-alkoxy-, $-C(=O)O-R^6$ or -OH groups;

or

when 2 $R^7$ groups are present ortho to each other on an aryl- or heteroaryl- ring, said 2 $R^7$ groups together form a bridge :

$*O(CH_2)_2O*$, $*O(CH_2)O*$, *NH(C(=O))NH*, wherein * represent the point of attachment to said aryl- or heteroaryl- ring ;

$R^8$ represents a hydrogen or halogen atom, or a -CN, $C_1$-$C_6$-alkoxy-, $C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})N$-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, $C_2$-$C_6$-alkenyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, -$C(=O)R^6$, -$C(=O)N(H)R^{6a}$, -$C(=O)N(R^{6a})R^{6b}$, -$C(=O)O$-$R^6$, -$N(R^{6a})R^{6b}$, -$NO_2$, -$N(H)C(=O)R^6$, -$N(R^{6c})C(=O)R^6$, -$N(H)C(=O)N(R^{6a})R^{6b}$, -$N(R^{6c})C(=O)N(R^{6a})R^{6b}$, -$N(H)C(=O)OR^6$, -$N(R^{6c})C(=O)OR^6$, -$N(H)S(=O)R^6$, -$N(R^{6c})S(=O)R^6$, -$N(H)S(=O)_2R^6$, -$N(R^{6c})S(=O)_2R^6$, -$N=S(=O)(R^{6a})R^{6b}$, -$OR^6$, -$O(C=O)R^6$, -$O(C=O)N(R^{6a})R^{6b}$, -$O(C=O)OR^6$, -$SR^6$, -$S(=O)R^6$, -$S(=O)N(H)R^6$, -$S(=O)N(R^{6a})R^{6b}$, -$S(=O)_2R^6$, -$S(=O)_2N(H)R^6$, -$S(=O)_2N(R^{6a})R^{6b}$, -$S(=O)(=NR^{6c})R^6$ or -$S(=O)_2$-(3- to 7-membered heterocycloalkyl) group;
wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 $C_1$-$C_6$-alkyl- groups ;

m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;

n is an integer of 0, 1, 2, 3, 4 or 5 ;

X represents $S(=O)_p$, O, $NR^6$, $CR^{6a}R^{6b}$ or $C=CR^{6a}R^{6b}$;

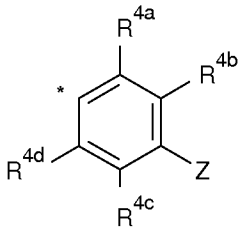
p is an integer of 0, 1 or 2 ;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

WO 2011/013729A1 and WO 2012/032031A1 disclose methods for preparing said compounds of general formula (I).

In a preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

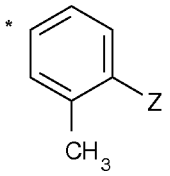
$R^A$ represents a



group.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

$R^A$ represents a



group;

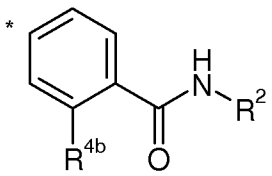
wherein * indicates the point of attachment of said groups with the rest of the molecule ; and

Z represents a -C(=O)N(H)$R^2$ or a -C(=S)N(H)$R^2$ group.

Preferably Z represents a -C(=O)N(H)$R^2$ group.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

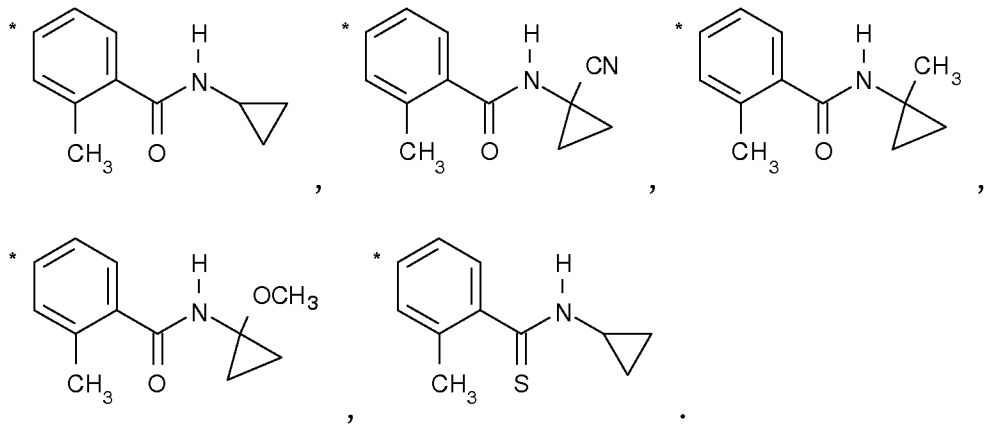
$R^A$ represents a



group;

wherein * indicates the point of attachment of said group with the rest of the molecule.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein $R^A$ is selected from the group consisting of:



In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

$R^2$ represents a hydrogen atom, or a $C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})N$-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, -$C_1$-$C_6$-alkyl-CN, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, $C_2$-$C_6$-alkenyl-, $C_2$-$C_6$-alkynyl- or $C_3$-$C_6$-cycloalkyl- group ;

wherein said $C_3$-$C_6$-cycloalkyl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 groups selected from: halogen, -OH, -CN, $C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy-, halo-$C_1$-$C_6$-alkyl-.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein $R^2$ represents a methyl-, ethyl- or cyclopropyl- group ;

wherein said methyl- or ethyl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 groups selected from: halogen, -OH, -CN, $C_1$-$C_3$-alkoxy- ;

wherein said cyclopropyl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 groups selected from: halogen, -OH, -CN, $C_1$-$C_3$-alkyl-, $C_1$-$C_3$-alkoxy-, HO-$C_1$-$C_3$-alkyl-, halo-$C_1$-$C_3$-alkyl-.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

$R^2$ represents a $C_3$-$C_6$-cycloalkyl- group ;

wherein said $C_3$-$C_6$-cycloalkyl- group is optionally substituted, identically or differently, with 1, 2, or 3 groups selected from:

halogen, -OH, -CN, -$C_1$-$C_6$-alkyl, -$C_1$-$C_6$-alkoxy.

Preferably, the $C_3$-$C_6$-cycloalkyl- group is a cyclopropyl- group.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

$R^2$ represents a cyclopropyl- group ;

wherein said cyclopropyl- group is substituted, identically or differently, with 1 or 2 groups selected from:

halogen, -CN, -$C_1$-$C_3$-alkyl, -$C_1$-$C_3$-alkoxy.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

$R^3$ represents

a substituted or unsubstituted aryl-X- group, or

a substituted or unsubstituted heteroaryl-X- group.

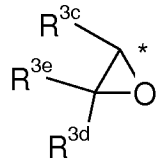
A preferred aryl-X- group is phenyl-X-.

Preferred heteroaryl-X- groups are quinolinyl-X-, pyridyl-X-, thienyl-X-, pyrazinyl-X-, imidazyl-X-, triazyl-X- and pyrazyl-X-. $R^3$ is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 $R^7$ groups. Preferably, $R^3$ is optionally substituted, identically or differently, with 1 or 2 $R^7$ groups.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein $R^3$ represents

$-C(R^{3a})(R^{3b})(R^{3c})$

or



;

wherein * indicates the point of attachment of said group with the rest of the molecule ;

wherein $R^{3a}$, $R^{3b}$ represent, independently from each other, a hydrogen atom or a halogen atom or a hydroxy-, $C_1$-$C_3$-alkyl-, HO-$C_1$-$C_3$-alkyl-, $C_2$-$C_4$-alkenyl-, halo-$C_1$-$C_3$-alkyl-, $C_1$-$C_3$-alkoxy- or halo-$C_1$-$C_3$-alkoxy- group, with the proviso that not both of $R^{3a}$ and $R^{3b}$ represent a hydrogen atom and not both of $R^{3a}$ and $R^{3b}$ represent a hydroxy group ;

or

$R^{3a}$, $R^{3b}$ together represent =O or $=C(R^{3d})(R^{3e})$ ;

or $R^{3a}$, $R^{3b}$ together with the carbon atom they are attached to, form a cyclopropyl- or cyclobutyl- ring ; wherein said cyclopropyl- or cyclobutyl- ring is optionally substituted, identically or differently, with 1 or 2 $R^{3d}$ groups ;

wherein $R^{3c}$ represents an aryl- or heteroaryl- group ; wherein said aryl- or heteroaryl- group is substituted, identically or differently, with 1, 2, 3 or 4 $R^7$ groups ;

and

wherein $R^{3d}$, $R^{3e}$ represent, independently from each other, a hydrogen atom or a $C_1$-$C_3$-alkyl- group.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

$R^{4a}$, $R^{4d}$ represent a hydrogen atom.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

$R^{4b}$ and $R^{4c}$ represent independently from each other, a hydrogen or halogen atom, or a -CN, -OH, $C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy- group; with the proviso that at least one of the groups $R^{4b}$ and $R^{4c}$ is not a hydrogen atom.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

$R^{4a}$, $R^{4c}$, $R^{4d}$ represent a hydrogen atom, and

$R^{4b}$ represents a hydrogen atom, a halogen atom, or a -CN, $C_1$-$C_3$-alkyl-, $C_1$-$C_3$-alkoxy-, halo-$C_1$-$C_3$-alkyl- or halo-$C_1$-$C_3$-alkoxy- group.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

$R^{4a}$, $R^{4c}$, $R^{4d}$ represent a hydrogen atom, and

$R^{4b}$ represents a hydrogen atom, halogen atom or a $C_1$-$C_3$-alkyl- group.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

$R^{4a}$, $R^{4c}$, $R^{4d}$ represent a hydrogen atom, and

$R^{4b}$ represents a $C_1$-$C_2$-alkyl- group.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

$R^{4a}$, $R^{4c}$, $R^{4d}$ represent a hydrogen atom, and

$R^{4b}$ represents a methyl- group.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

$R^5$ represents a hydrogen atom or a $C_1$-$C_6$-alkyl-, -$(CH_2)_n$-$C_2$-$C_6$-alkenyl, -$(CH_2)_n$-$C_2$-$C_6$-alkynyl, -$(CH_2)_m$-$C_3$-$C_6$-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-$C_1$-$C_6$-alkyl-, heteroaryl-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})$N-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, -$C_1$-$C_6$-alkyl-CN, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, $C_3$-$C_6$-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, $C_4$-$C_8$-cycloalkenyl-, aryl- or heteroaryl- group ;
wherein said $C_1$-$C_6$-alkyl-, -$(CH_2)_n$-$C_2$-$C_6$-alkenyl, -$(CH_2)_n$-$C_2$-$C_6$-alkynyl, -$(CH_2)_m$-$C_3$-$C_6$-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-$C_1$-$C_6$-alkyl-, heteroaryl-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})$N-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, -$C_1$-$C_6$-alkyl-CN, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, $C_3$-$C_6$-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, $C_4$-$C_8$-cycloalkenyl-, aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 $R^8$ groups.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

$R^5$ represents a $C_1$-$C_6$-alkyl-, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl- or heteroaryl- group ;
wherein said $C_1$-$C_6$-alkyl-, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-, heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 $R^8$ groups.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

$R^6$, $R^{6a}$, $R^{6b}$, and $R^{6c}$ represent, independently from each other, a hydrogen atom, or a $C_1$-$C_6$-alkyl- group.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

$R^7$ represents a hydrogen or halogen atom, or an HO-, -CN, $C_1$-$C_6$-alkoxy-, $C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, aryl-, heteroaryl-, -$C(=O)N(R^{6a})R^{6b}$, -$N(H)C(=O)R^6$, -$N(H)C(=O)N(R^{6a})R^{6b}$, -$OR^6$, -$S(=O)R^6$, or -$S(=O)_2R^6$, group ; wherein said $C_1$-$C_6$-alkoxy- or heteroaryl- group is optionally substituted, identically or differently, with a $C_1$-$C_4$-alkyl-, halo-$C_1$-$C_6$-alkoxy-, -$C(=O)O$-$R^6$ or -OH group;
or
when 2 $R^7$ groups are present ortho- to each other on an aryl- or heteroaryl- ring, said 2 $R^7$ groups together form a bridge : *$O(CH_2)_2O$*, *$O(CH_2)O$*, *$NH(C(=O))NH$*, wherein * represent the point of attachment to said aryl- or heteroaryl- ring.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

$R^7$ represents a halogen atom, or a hydroxy-, -CN, $C_1$-$C_6$-alkoxy-, $C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})N$-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl- group.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

$R^8$ represents a hydrogen or halogen atom or a -CN, $C_1$-$C_6$-alkoxy-, $C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})N$-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, $C_2$-$C_6$-alkenyl-, $C_2$-$C_6$-alkynyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, -$C(=O)R^6$, -$C(=O)N(H)R^{6a}$, -$C(=O)N(R^{6a})R^{6b}$, -$C(=O)O$-$R^6$, -$N(R^{6a})R^{6b}$, -$NO_2$, -$N(H)C(=O)R^6$, -$N(R^{6c})C(=O)R^6$, -$N(H)C(=O)N(R^{6a})R^{6b}$, -$N(R^{6c})C(=O)N(R^{6a})R^{6b}$, -$N(H)C(=O)OR^6$, -$N(R^{6c})C(=O)OR^6$, -$N(H)S(=O)R^6$,

$-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O_2)R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ or $-S(=O)_2$-(3- to 7-membered heterocycloalkyl) group ;

wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 $C_1$-$C_6$-alkyl- groups.

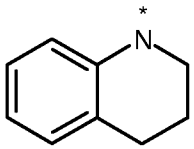
In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

$R^8$ represents a halogen atom, a -CN, $-N(R^{6a})R^{6b}$, or $-OR^6$ group.

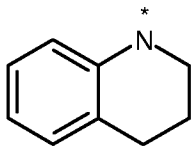
In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

X is S, S(=O), $S(=O)_2$, O, $NR^6$, $CR^{6a}R^{6b}$ or $C=CR^{6a}R^{6b}$.

It should be noted that in the case of $R^3$ being a substituted aryl-X- group or a substituted heteroaryl-X- group and X being $NR^6$, the substituent $R^6$ optionally can be attached to the aryl- or heteroaryl- ring, thereby - together with the N-atom - forming a heterocyclic ring fused to the aryl- or heteroaryl- ring. An example of such a fused ring system is the group :

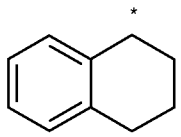



, in which * indicates the point of attachment of said group with the rest of the molecule. In other words, a group with the formula

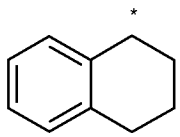



, in which * indicates the point of attachment of said group with the rest of the molecule, is an example of a substituted aryl-X- group.

Accordingly, in a group of formula aryl-$CR^{6a}R^{6b}$- or heteroaryl-$CR^{6a}R^{6b}$-, the substituents $R^{6a}$ and/or $R^{6b}$ optionally can be attached to the aryl- or heteroaryl- ring, thereby forming one or more carbocyclic rings fused to the aryl- or heteroaryl- ring. An example of such a fused ring system is the group



, in which * indicates the point of attachment of said group with the rest of the molecule. In other words, a group with the formula



, in which * indicates the point of attachment of said group with the rest of the molecule, is another example of a substituted aryl-X- group.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

X is S, S(=O), or $S(=O)_2$.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

X is O.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

X is $NR^6$. Preferably, X is NH or $N(CH_3)$. Most preferably, X is NH.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

X is $CR^{6a}R^{6b}$. Preferably X is $CH_2$.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

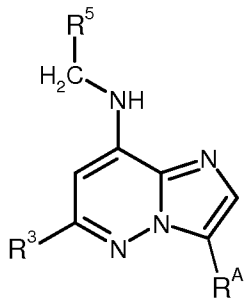
X is $C=CR^{6a}R^{6b}$. Preferably X is $C=CH_2$.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

m is an integer of 0, 1 or 2.

It is to be understood that the present invention relates also to any combination of the preferred embodiments of compounds A described above. Some examples of combinations of the embodiments of compound A are given hereinafter. However, the invention is not limited to these combinations.

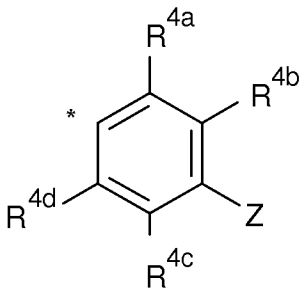
In another preferred embodiment, compound A is selected from the group of compounds of general formula (I)



(I)

wherein

the $R^A$ represents




;

wherein * indicates the point of attachment of said groups with the rest of the molecule ;

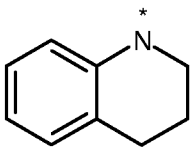
Z represents a -C(=O)N(H)$R^2$ or a -C(=S)N(H)$R^2$ group ;

$R^2$ represents a hydrogen atom, or a $C_1$-$C_6$-alkyl- or $C_3$-$C_6$-cycloalkyl- group ;

wherein said $C_1$-$C_6$-alkyl- or $C_3$-$C_6$-cycloalkyl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 groups selected from:

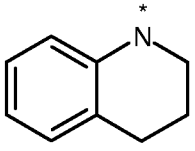
halogen, -OH, -CN, -$C_1$-$C_6$-alkyl, -$C_1$-$C_6$-alkoxy ;

$R^3$ represents an aryl-X- or a heteroaryl-X- group, or a




group, in which * indicates the point of attachment of said group with the rest of the molecule ;

wherein said aryl-X-, heteroaryl-X- or




group

is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 $R^7$ groups ;

$R^{4a}$, $R^{4b}$, $R^{4c}$, $R^{4d}$

represent, independently from each other, a hydrogen or halogen atom, or a -CN, -OH, $C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy-, halo-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-, $R^{6a}(R^{6b})$N-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, NC-$C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl- group;
with the proviso that at least one of the groups $R^{4b}$ and $R^{4c}$ is not a hydrogen atom;

$R^5$ represents a hydrogen atom, or a $C_1$-$C_6$-alkyl-, -$(CH_2)_n$-$C_2$-$C_6$-alkenyl, -$(CH_2)_n$-$C_2$-$C_6$-alkynyl, -$(CH_2)_m$-$C_3$-$C_6$-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-$C_1$-$C_6$-alkyl-, heteroaryl-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})$N-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, -$C_1$-$C_6$-alkyl-CN, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, $C_3$-$C_6$-cycloalkyl-, 3- to 7-membered heterocycloalkyl, $C_2$-$C_6$-alkenyl-, $C_4$-$C_8$-cycloalkenyl-, $C_2$-$C_6$-alkynyl-, aryl- or heteroaryl- group ;
said $C_1$-$C_6$-alkyl-, -$(CH_2)_n$-$C_2$-$C_6$-alkenyl, -$(CH_2)_n$-$C_2$-$C_6$-alkynyl, -$(CH_2)_m$-$C_3$-$C_6$-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-$C_1$-$C_6$-alkyl-, heteroaryl-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})$N-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, -$C_1$-$C_6$-alkyl-CN, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, $C_3$-$C_6$-cycloalkyl-, 3- to 7-membered heterocycloalkyl, $C_4$-$C_8$-cycloalkenyl-, aryl- or heteroaryl- group
is optionally substituted, identically or differently, with 1, 2, 3, or 4 $R^8$ groups ;

$R^6$, $R^{6a}$, $R^{6b}$, $R^{6c}$,

represent, independently from each other, a hydrogen atom, or a $C_1$-$C_6$-alkyl, HO-$C_1$-$C_6$-alkyl-, $C_3$-$C_6$-cycloalkyl, $C_2$-$C_6$-alkenyl, 3- to 7-membered heterocycloalkyl, aryl, heteroaryl, aryl-$C_1$-$C_6$-alkyl-, or heteroaryl-$C_1$-$C_6$-alkyl- group ;

$R^7$ represents a hydrogen or halogen atom, or a HO-, -CN, $C_1$-$C_6$-alkoxy-, $C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})N$-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, $H_2N$-$C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, $C_2$-$C_6$-alkenyl, 3- to 7-membered heterocycloalkyl, aryl-, heteroaryl-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, or $-S(=O)(=NR^{6c})R^6$ group ;

wherein said $C_1$-$C_6$-alkoxy-, aryl-, 3- to 7-membered heterocycloalkyl, or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, or 3 $C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy-, halo-$C_1$-$C_6$-alkoxy-, $-C(=O)O-R^6$ or -OH groups;

or

when 2 $R^7$ groups are present ortho to each other on an aryl or heteroarly ring, said 2 $R^7$ groups together form a bridge :
$*O(CH_2)_2O*$, $*O(CH_2)O*$, $*CH_2(CH_2)_2NH*$, $*CH_2CH_2N(R^{6a})CH_2*$, *NH(C(=O))NH*, *C(H)=C(H)-C(=O)-N(H)*,
wherein * represent the point of attachment to said aryl or heteroaryl ring ;

$R^8$ represents a hydrogen or halogen atom, or a -CN, -OH, $C_1$-$C_6$-alkoxy-, $C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})N$-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, $C_2$-$C_6$-alkenyl, 3- to 7-membered heterocycloalkyl, aryl-, heteroaryl-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2OH$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ group , $-S(=O)_2$-(3- to 7-membered heterocycloalkyl);
wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 $C_1$-$C_6$-alkyl- groups ;

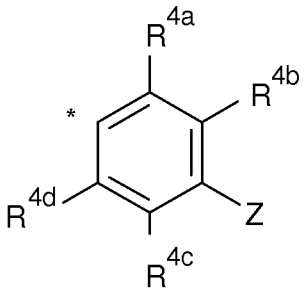
m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;

n is an integer of 0, 1, 2, 3, 4 or 5 ; and

X is S, S(=O), $S(=O)_2$, O, $NR^6$, $CR^{6a}R^{6b}$, $C=CR^{6a}R^{6b}$.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

$R^A$ represents



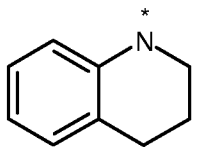

;

wherein * indicates the point of attachment of said groups with the rest of the molecule ;

Z represents a -C(=O)N(H)$R^2$ or a -C(=S)N(H)$R^2$ group ;

$R^2$ represents a $C_1$-$C_3$-alkyl- or $C_3$-$C_6$-cycloalkyl- group ;
wherein said $C_1$-$C_3$-alkyl- or $C_3$-$C_6$-cycloalkyl- group is optionally substituted, identically or differently, with 1, 2 or 3 groups selected from:
halogen, -OH, -CN, -$C_1$-$C_6$-alkyl, -$C_1$-$C_6$-alkoxy ;

$R^3$ represents a group selected from:
phenyl-X, quinolinyl-X-, pyridyl-X-, thienyl-X-, pyrazinyl-X-, imidazyl-X-, triazyl-X-, pyrazyl-X- and



;

wherein said group is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 $R^7$ groups ;

$R^{4a}$ represents hydrogen;

$R^{4d}$ represents hydrogen;

one of the groups $R^{4b}$ and $R^{4c}$ represents a hydrogen atom while the other one represents halo- or a $C_1$-$C_6$-alkyl- group;

$R^5$ represents a hydrogen atom, or a $C_1$-$C_6$-alkyl-, -$(CH_2)_n$-$C_2$-$C_6$-alkenyl, -$(CH_2)_n$-$C_2$-$C_6$-alkynyl, -$(CH_2)_m$-$C_3$-$C_6$-cycloalkyl, -$(CH_2)_m$-(3- to

7-membered heterocycloalkyl), aryl-$C_1$-$C_6$-alkyl-, heteroaryl-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})N$-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, -$C_1$-$C_6$-alkyl-CN, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, $C_3$-$C_6$-cycloalkyl-, 3- to 7-membered heterocycloalkyl, $C_2$-$C_6$-alkenyl-, $C_4$-$C_8$-cycloalkenyl-, $C_2$-$C_6$-alkynyl-, aryl- or heteroaryl- group ;

said $C_1$-$C_6$-alkyl-, -$(CH_2)_n$-$C_2$-$C_6$-alkenyl, -$(CH_2)_n$-$C_2$-$C_6$-alkynyl, -$(CH_2)_m$-$C_3$-$C_6$-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-$C_1$-$C_6$-alkyl-, heteroaryl-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})N$-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, -$C_1$-$C_6$-alkyl-CN, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, $C_3$-$C_6$-cycloalkyl-, 3- to 7-membered heterocycloalkyl, $C_4$-$C_8$-cycloalkenyl-, aryl- or heteroaryl- group

is optionally substituted, identically or differently, with 1, 2, 3, or 4 $R^8$ groups ;

$R^6$, $R^{6a}$, $R^{6b}$, $R^{6c}$

represent, independently from each other, a hydrogen atom, or a $C_1$-$C_6$-alkyl, HO-$C_1$-$C_6$-alkyl-, $C_3$-$C_6$-cycloalkyl, $C_2$-$C_6$-alkenyl, 3- to 7-membered heterocycloalkyl, aryl, heteroaryl, aryl-$C_1$-$C_6$-alkyl-, or heteroaryl-$C_1$-$C_6$-alkyl- group ;

$R^7$ represents a hydrogen or halogen atom, or a HO-, -CN, $C_1$-$C_6$-alkoxy-, $C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})N$-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, $H_2N$-$C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, $C_2$-$C_6$-alkenyl, 3- to 7-membered heterocycloalkyl, aryl-, heteroaryl-, -C(=O)$R^6$, -C(=O)N(H)$R^{6a}$, -C(=O)N($R^{6a}$)$R^{6b}$, -C(=O)O-$R^6$, -N($R^{6a}$)$R^{6b}$, -$NO_2$, -N(H)C(=O)$R^6$, -N($R^{6c}$)C(=O)$R^6$, -N(H)C(=O)N($R^{6a}$)$R^{6b}$, -N($R^{6c}$)C(=O)N($R^{6a}$)$R^{6b}$, -N(H)C(=O)O$R^6$, -N($R^{6c}$)C(=O)O$R^6$, -N(H)S(=O)$R^6$, -N($R^{6c}$)S(=O)$R^6$, -N(H)S(=O)$_2$$R^6$, -N($R^{6c}$)S(=O)$_2$$R^6$, -N=S(=O)($R^{6a}$)$R^{6b}$, -O$R^6$, -O(C=O)$R^6$,

-O(C=O)N($R^{6a}$)$R^{6b}$, -O(C=O)O$R^6$, -S$R^6$, -S(=O)$R^6$, - S(=O)N(H)$R^6$, -S(=O)N($R^{6a}$)$R^{6b}$, -S(=O)$_2$$R^6$, - S(=O)$_2$N(H)$R^6$, -S(=O)$_2$N($R^{6a}$)$R^{6b}$, or -S(=O)(=N$R^{6c}$)$R^6$ group ;

wherein said $C_1$-$C_6$-alkoxy-, aryl-, 3- to 7-membered heterocycloalkyl, or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, or 3 $C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy-, halo-$C_1$-$C_6$-alkoxy-, -C(=O)O-$R^6$ or -OH groups;

or

when 2 $R^7$ groups are present ortho to each other on an aryl or heteroarly ring, said 2 $R^7$ groups together form a bridge :

*O($CH_2$)$_2$O*, *O($CH_2$)O*, *$CH_2$($CH_2$)$_2$NH*, *$CH_2CH_2$N($R^{6a}$)$CH_2$*, *NH(C(=O))NH*, *C(H)=C(H)-C(=O)-N(H)*,

wherein * represent the point of attachment to said aryl or heteroaryl ring ;

$R^8$ represents a hydrogen or halogen atom, or a -CN, -OH, $C_1$-$C_6$-alkoxy-, $C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}$($R^{6b}$)N-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, $C_2$-$C_6$-alkenyl, 3- to 7-membered heterocycloalkyl, aryl-, heteroaryl-, -C(=O)$R^6$, -C(=O)N(H)$R^{6a}$,

-C(=O)N($R^{6a}$)$R^{6b}$, -C(=O)O-$R^6$, -N($R^{6a}$)$R^{6b}$, -$NO_2$, -N(H)C(=O)$R^6$, -N($R^{6c}$)C(=O)$R^6$,

-N(H)C(=O)N($R^{6a}$)$R^{6b}$, -N($R^{6c}$)C(=O)N($R^{6a}$)$R^{6b}$, -N(H)C(=O)O$R^6$, -N($R^{6c}$)C(=O)O$R^6$, -N(H)S(=O)$R^6$, -N($R^{6c}$)S(=O)$R^6$, -N(H)S(=O)$_2$$R^6$, -N($R^{6c}$)S(=O)$_2$$R^6$, -N=S(=O)($R^{6a}$)$R^{6b}$, -O$R^6$, -O(C=O)$R^6$, -O(C=O)N($R^{6a}$)$R^{6b}$, -O(C=O)O$R^6$, -S$R^6$, -S(=O)$R^6$, -S(=O)N(H)$R^6$, -S(=O)N($R^{6a}$)$R^{6b}$, -S(=O)$_2$$R^6$, -S(=O)$_2$OH, -S(=O)$_2$N(H)$R^6$, -S(=O)$_2$N($R^{6a}$)$R^{6b}$, -S(=O)(=N$R^{6c}$)$R^6$ group , -S(=O)$_2$-(3- to 7-membered heterocycloalkyl);

wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, or 4 $C_1$-$C_6$-alkyl- groups ;

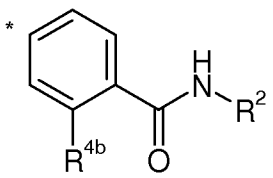
m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;

n is an integer of 0, 1, 2, 3, 4 or 5 ; and

X is S, S(=O), $S(=O)_2$, O, $NR^6$, $CR^{6a}R^{6b}$, $C=CR^{6a}R^{6b}$.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

$R^A$ represents



wherein * indicates the point of attachment of said group with the rest of the molecule ;

$R^2$ represents a methyl-, ethyl- or cyclopropyl- group ;

wherein said methyl- or ethyl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 groups selected from: halogen, -OH, -CN, $C_1$-$C_3$-alkoxy- ;

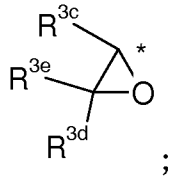
wherein said cyclopropyl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 groups selected from: halogen, -OH, -CN, $C_1$-$C_3$-alkyl-, $C_1$-$C_3$-alkoxy-, HO-$C_1$-$C_3$-alkyl-, halo-$C_1$-$C_3$-alkyl- ;

$R^3$ represents

$-C(R^{3a})(R^{3b})(R^{3c})$ ;

or

$R^3$ represents



;

wherein * indicates the point of attachment of said group with the rest of the molecule ;

$R^{3a}$, $R^{3b}$

represent, independently from each other, a hydrogen atom or a halogen atom or a hydroxy-, $C_1$-$C_3$-alkyl-, HO-$C_1$-$C_3$-alkyl-, $C_2$-$C_4$-alkenyl-, halo-$C_1$-$C_3$-alkyl-, $C_1$-$C_3$-alkoxy- or halo-$C_1$-$C_3$-alkoxy- group, with the proviso that not both of $R^{3a}$ and $R^{3b}$ represent a hydrogen atom and not both of $R^{3a}$ and $R^{3b}$ represent a hydroxy group ;

or

$R^{3a}$, $R^{3b}$

together represent =O or =C($R^{3d}$)($R^{3e}$) ;

or

$R^{3a}$, $R^{3b}$

together with the carbon atom they are attached to, form a cyclopropyl- or cyclobutyl- ring ;
wherein said cyclopropyl- or cyclobutyl- ring is optionally substituted, identically or differently, with 1 or 2 $R^{3d}$ groups;

$R^{3c}$ represents an aryl- or heteroaryl- group ;
wherein said aryl- or heteroaryl- group is substituted, identically or differently, with 1, 2, 3 or 4 $R^7$ groups ;

$R^{3d}$, $R^{3e}$

represent, independently from each other, a hydrogen atom or a $C_1$-$C_3$-alkyl- group ;

$R^{4b}$ represents a hydrogen atom, a halogen atom, or a -CN, $C_1$-$C_3$-alkyl-, $C_1$-$C_3$-alkoxy-, halo-$C_1$-$C_3$-alkyl- or halo-$C_1$-$C_3$-alkoxy- group ;

$R^5$ represents a hydrogen atom or a $C_1$-$C_6$-alkyl-, -$(CH_2)_n$-$C_2$-$C_6$-alkenyl, -$(CH_2)_n$-$C_2$-$C_6$-alkynyl, -$(CH_2)_m$-$C_3$-$C_6$-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-$C_1$-$C_6$-alkyl-, heteroaryl-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})$N-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, -$C_1$-$C_6$-alkyl-CN, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, $C_3$-$C_6$-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, $C_4$-$C_8$-cycloalkenyl-, aryl- or heteroaryl- group ;
wherein said $C_1$-$C_6$-alkyl-, -$(CH_2)_n$-$C_2$-$C_6$-alkenyl, -$(CH_2)_n$-$C_2$-$C_6$-alkynyl, -$(CH_2)_m$-$C_3$-$C_6$-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-$C_1$-$C_6$-alkyl-, heteroaryl-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})$N-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, -$C_1$-$C_6$-alkyl-CN, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, $C_3$-$C_6$-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, $C_4$-$C_8$-cycloalkenyl-, aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 $R^8$ groups ;

$R^6$, $R^{6a}$, $R^{6b}$
represent, independently from each other, a hydrogen atom or a $C_1$-$C_6$-alkyl- group ;

$R^7$ represents a halogen atom, or a hydroxy-, -CN, $C_1$-$C_6$-alkoxy-, $C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})$N-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl- group ;

$R^8$ represents a hydrogen or halogen atom or a -CN, $C_1$-$C_6$-alkoxy-, $C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})$N-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, $C_2$-$C_6$-alkenyl-,

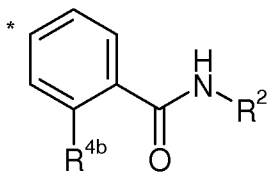
$C_2$-$C_6$-alkynyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)$R^6$, -C(=O)N(H)$R^{6a}$, -C(=O)N($R^{6a}$)$R^{6b}$, -C(=O)O-$R^6$, -N($R^{6a}$)$R^{6b}$, -$NO_2$, -N(H)C(=O)$R^6$, -N($R^{6c}$)C(=O)$R^6$, -N(H)C(=O)N($R^{6a}$)$R^{6b}$, -N($R^{6c}$)C(=O)N($R^{6a}$)$R^{6b}$, -N(H)C(=O)O$R^6$, -N($R^{6c}$)C(=O)O$R^6$, -N(H)S(=O)$R^6$, -N($R^{6c}$)S(=O)$R^6$, -N(H)S(=O)$_2$$R^6$, -N($R^{6c}$)S(=O)$_2$$R^6$, -N=S(=O)($R^{6a}$)$R^{6b}$, -O$R^6$, -O(C=O)$R^6$, -O(C=O)N($R^{6a}$)$R^{6b}$, -O(C=O)O$R^6$, -S$R^6$, -S(=O)$R^6$, - S(=O)N(H)$R^6$, -S(=O)N($R^{6a}$)$R^{6b}$, -S(=$O_2$)$R^6$, -S(=O)$_2$N(H)$R^6$, -S(=O)$_2$N($R^{6a}$)$R^{6b}$, -S(=O)(=N$R^{6c}$)$R^6$ or -S(=O)$_2$-(3- to 7-membered heterocycloalkyl) group ; wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 $C_1$-$C_6$-alkyl- groups ;

m is an integer of 0, 1 or 2 ;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

$R^A$ represents



wherein * indicates the point of attachment of said group with the rest of the molecule ;

$R^2$ represents a cyclopropyl- group ;

$R^3$ represents
$-C(R^{3a})(R^{3b})(R^{3c})$ ;

$R^{3a}$, $R^{3b}$
represent, independently from each other, a hydrogen atom or a halogen atom, with the proviso that not both of $R^{3a}$ and $R^{3b}$ represent a hydrogen atom ;

or

$R^{3a}$, $R^{3b}$
together represent =O or $=CH_2$ ;

$R^{3c}$ represents an phenyl- group ;
wherein said phenyl- group is substituted, identically or differently, with 1, 2 or 3 $R^7$ groups ;

$R^{4b}$ represents a hydrogen atom, a halogen atom, or a -CN, $C_1$-$C_3$-alkyl-, $C_1$-$C_3$-alkoxy-, halo-$C_1$-$C_3$-alkyl- or halo-$C_1$-$C_3$-alkoxy- group ;

$R^5$ represents a $C_1$-$C_6$-alkyl-, $-(CH_2)_m$-(3- to 7-membered heterocycloalkyl), $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl- or halo-$C_1$-$C_6$-alkyl- group ;
wherein said $-(CH_2)_m$-(3- to 7-membered heterocycloalkyl) group is optionally substituted, identically or differently, with 1, 2 or 3 $R^8$ groups ;

$R^6$, $R^{6a}$, $R^{6b}$
represent, independently from each other, a hydrogen atom or a $C_1$-$C_6$-alkyl- group ;

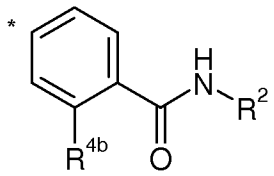
$R^7$ represents a halogen atom, or a hydroxy-, -CN, $C_1$-$C_6$-alkoxy-, $C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})N$-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl- group ;

$R^8$ represents a halogen atom, or a -CN, hydroxy-, $C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy- or halo-$C_1$-$C_6$-alkoxy- group;
wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 $C_1$-$C_6$-alkyl- groups ;

m is an integer of 0, 1 or 2.

In another preferred embodiment, compound A is selected from the group of compounds of general formula (I), *supra*, wherein

$R^A$ represents



wherein * indicates the point of attachment of said group with the rest of the molecule ;

$R^2$ represents a cyclopropyl- group ;
wherein said cyclopropyl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 groups selected from: halogen, -OH, -CN, $C_1$-$C_3$-alkyl-, $C_1$-$C_3$-alkoxy-, HO-$C_1$-$C_3$-alkyl-, halo-$C_1$-$C_3$-alkyl-;

$R^3$ represents
$-C(R^{3a})(R^{3b})(R^{3c})$ ;

$R^{3a}$, $R^{3b}$

represent, independently from each other, a hydrogen atom, or a halogen atom or a hydroxy- or $C_1$-$C_3$-alkyl- group, with the proviso that not both of $R^{3a}$ and $R^{3b}$ represent a hydrogen atom and not both of of $R^{3a}$ and $R^{3b}$ represent a hydroxy group;

or

$R^{3a}$, $R^{3b}$

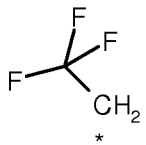
together represent =O or $=CH_2$ ;

$R^{3c}$ represents a phenyl- group ;

wherein said phenyl- group is substituted, identically or differently, with 1, 2 or 3 $R^7$ groups ;

$R^{4b}$ represents a methyl- group ;

$R^5$ represents




wherein * indicates the point of attachment of said group with the rest of the molecule ;

$R^7$ represents a halogen atom, or a HO- or $C_1$-$C_3$-alkoxy- group ;

$R^8$ represents a halogen atom or a $C_1$-$C_3$-alkyl- group.

In another preferred embodiment, compound A is selected from the group of Examples disclosed in WO 2012/032031A1.

In another preferred embodiment, compound A is selected from the group of compounds of Formula (I') or of Formula (I) as described and defined in WO 2011/013729A1.

In another preferred embodiment, compound A is selected from the group of Examples disclosed in WO 2011/013729A1.

In another preferred embodiment, compound A is selected from the group of Examples 2-1 to 2-233 disclosed in WO 2011/013729A1.

In a another preferred embodiment compound A is selected from the compounds A of the present invention specified in the Experimental Section below.

The synergistic behavior of a combination of the present invention is demonstrated herein with distinct siRNAs that deplete one of the three anti-apoptotic multidomain proteins of the Bcl-2 family (Bcl-2, Bcl-XL, Mcl-1).

This makes it evident, that principially any inhibitors of anti-apoptotic proteins of the Bcl-2 family can be used in a combination of the present invention.

So, compound B can be selected from inhibitors of an anti-apoptotic protein of the Bcl-2 family specifically or generically disclosed e.g. in the following publications which are incorporated herein by reference: US 8,188,077 B2; C. Bodur and H. Basaga, Bcl-2 Inhibitors: Emerging Drugs in Cancer Therapy, Current Medicinal Chemistry, 2012, 19, 1804-1820; Mohammad, R. M., et al. Preclinical studies of TW-37, a new nonpeptidic small-molecule inhibitor of Bcl-2, in diffuse large cell lymphoma xenograft model reveal drug action on both Bcl-2 and Mcl-1. Clin. Cancer Res. 13, 2226-2235, 2007.

Compound B can be selected from the group of compounds consisting of: B717/LIC-101 complex (Nippon Shinyaku Co. Ltd.), bcl-2 inhibiting siRNA/LIC-24 liposome complex (Nippon Shinyaku Co. Ltd.), beclanorsen (Santaris Pharma A/S), VMD-8018 (VM Discovery Inc.), oblimersen (Genta Inc.), apogossypol (Sanford-Burnham Medical Research Institute), 1133719 (Kirin Brewery Co. Ltd.), PNT-100 (ProNAi Therapeutics Inc.), HG-1113 (Human Genome Sciences Inc.), S-44563 (Servier), ABT-731 (Abbott Laboratories), modified HA14-1 compounds (GL Pharmaceutical Inc.), ONT-701 (Sanford-Burnham Medical Research Institute), gossypol derivatives (INSERM), BP-100-1.02 (Bio-Path Holdings Inc.), obatoclax (Gemin X Pharmaceuticals Inc.), navitoclax (Abbott Laboratories), AT-101 (University of Michigan).

Preferably, compound B is selected from the group consisting of: Obatoclax (GX-15-070), Navitoclax (ABT-263), TW-37, B717/LIC-101 complex, beclanorsen, VMD-8018, oblimersen, apogossypol, 1133719, PNT-100, HG-1113, S-44563, ABT-731, ONT-701, BP-100-1.02, AT-101.

In accordance with an embodiment, the present invention relates to a combination of any component A mentioned herein with any component B mentioned herein, optionally with any component C mentioned herein.

In a particular embodiment, the present invention relates to a combination of a component A with a component B, optionally with a component C, as mentioned in the Examples Section herein.

Further, the present invention relates to :

a kit comprising :

- a combination of :

component A : one or more Mps-1 kinase inhibitors, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ;

component B : one or more inhibitors of an anti-apoptotic protein from the Bcl-2 family, or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof ; and, optionally,

component C : one or more further pharmaceutical agents ;

in which optionally either or both of said components A and B in any of the above-mentioned combinations are in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially. The components may be administered independnently of one another by the oral, intravenous, topical, local installations, intraperitoneal or nasal route.

Either or both of components A and B of any of the combinations of the present invention may be in a useful form, such as pharmaceutically acceptable salts, co-precipitates, metabolites, hydrates, solvates and prodrugs of all the compounds of examples. The term “pharmaceutically acceptable salt" refers to a relatively non-toxic, inorganic or organic acid addition salt of a compound of the present invention. For example, see S. M. Berge, *et al*. “Pharmaceutical Salts,” *J. Pharm. Sci*. 1977, 66, 1-19. Pharmaceutically acceptable salts include those obtained by reacting the main compound, functioning as a base, with an inorganic or organic acid to form a salt, for example, salts of hydrochloric acid, sulfuric acid, phosphoric acid, methane sulfonic acid, camphor sulfonic acid, oxalic acid, maleic acid, succinic acid and citric acid. Pharmaceutically acceptable salts also include those in which the main compound functions as an acid and is reacted with an appropriate base to form, e.g., sodium, potassium, calcium, magnesium, ammonium, and chorine salts. Those skilled in the art will further recognize

that acid addition salts of the claimed compounds may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts of acidic compounds of the invention are prepared by reacting the compounds of the invention with the appropriate base via a variety of known methods.

Representative salts of the compounds of this invention include the conventional non-toxic salts and the quaternary ammonium salts which are formed, for example, from inorganic or organic acids or bases by means well known in the art. For example, such acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cinnamate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, chloride, bromide, iodide, 2-hydroxyethanesulfonate, itaconate, lactate, maleate, mandelate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, sulfonate, sulfate, tartrate, thiocyanate, tosylate, and undecanoate.

Base salts include alkali metal salts such as potassium and sodium salts, alkaline earth metal salts such as calcium and magnesium salts, and ammonium salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine. Additionally, basic nitrogen containing groups may be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, or butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl sulfate, or diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and strearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

A solvate for the purpose of this invention is a complex of a solvent and a compound of the invention in the solid state. Exemplary solvates would include, but are not limited to, complexes of a compound of the invention with ethanol or methanol. Hydrates are a specific form of solvate wherein the solvent is water.

Compositions of this invention may be tableted with conventional tablet bases such as lactose, sucrose and cornstarch in combination with binders such as acacia, corn starch or gelatin, disintegrating agents intended to assist the break-up and dissolution of the tablet following administration such as potato starch, alginic acid, corn starch, and guar gum, gum tragacanth, acacia, lubricants intended to improve the flow of tablet granulation and to prevent the adhesion of tablet material to the surfaces of the tablet dies and punches, for example talc, stearic acid, or magnesium, calcium or zinc stearate, dyes, coloring agents, and flavoring agents such as peppermint, oil of wintergreen, or cherry flavoring, intended to enhance the aesthetic qualities of the tablets and make them more acceptable to the patient. Suitable excipients for use in oral liquid dosage forms include dicalcium phosphate and diluents such as water and alcohols, for example, ethanol, benzyl alcohol, and polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent or emulsifying agent. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance tablets, pills or capsules may be coated with shellac, sugar or both.

Dispersible powders and granules are suitable for the preparation of an aqueous suspension. They provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for

example those sweetening, flavoring and coloring agents described above, may also be present.

The pharmaceutical compositions of this invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil such as liquid paraffin or a mixture of vegetable oils. Suitable emulsifying agents may be (1) naturally occurring gums such as gum acacia and gum tragacanth, (2) naturally occurring phosphatides such as soy bean and lecithin, (3) esters or partial esters derived form fatty acids and hexitol anhydrides, for example, sorbitan monooleate, (4) condensation products of said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil such as, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as, for example, beeswax, hard paraffin, or cetyl alcohol. The suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate; one or more coloring agents; one or more flavoring agents; and one or more sweetening agents such as sucrose or saccharin.

Syrups and elixirs may be formulated with sweetening agents such as, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, and preservative, such as methyl and propyl parabens and flavoring and coloring agents.

The combinations of this invention may also be administered parenterally, that is, subcutaneously, intravenously, intraocularly, intrasynovially, intramuscularly, or interperitoneally, as injectable dosages of the compound in preferably a physiologically acceptable diluent with a pharmaceutical

carrier which can be a sterile liquid or mixture of liquids such as water, saline, aqueous dextrose and related sugar solutions, an alcohol such as ethanol, isopropanol, or hexadecyl alcohol, glycols such as propylene glycol or polyethylene glycol, glycerol ketals such as 2,2-dimethyl-1,1-dioxolane-4-methanol, ethers such as poly(ethylene glycol) 400, an oil, a fatty acid, a fatty acid ester or, a fatty acid glyceride, or an acetylated fatty acid glyceride, with or without the addition of a pharmaceutically acceptable surfactant such as a soap or a detergent, suspending agent such as pectin, carbomers, methycellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agent and other pharmaceutical adjuvants.

Illustrative of oils which can be used in the parenteral formulations of this invention are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, sesame oil, cottonseed oil, corn oil, olive oil, petrolatum and mineral oil. Suitable fatty acids include oleic acid, stearic acid, isostearic acid and myristic acid. Suitable fatty acid esters are, for example, ethyl oleate and isopropyl myristate. Suitable soaps include fatty acid alkali metal, ammonium, and triethanolamine salts and suitable detergents include cationic detergents, for example dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates; anionic detergents, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates; non-ionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and poly(oxyethylene-oxypropylene)s or ethylene oxide or propylene oxide copolymers; and amphoteric detergents, for example, alkyl-beta-aminopropionates, and 2-alkylimidazoline quarternary ammonium salts, as well as mixtures.

The parenteral compositions of this invention will typically contain from about 0.5% to about 25% by weight of the active ingredient in solution. Preservatives and buffers may also be used advantageously. In order to minimize or eliminate irritation at the site of injection, such compositions may contain a

non-ionic surfactant having a hydrophile-lipophile balance (HLB) preferably of from about 12 to about 17. The quantity of surfactant in such formulation preferably ranges from about 5% to about 15% by weight. The surfactant can be a single component having the above HLB or can be a mixture of two or more components having the desired HLB.

Illustrative of surfactants used in parenteral formulations are the class of polyethylene sorbitan fatty acid esters, for example, sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

The pharmaceutical compositions may be in the form of sterile injectable aqueous suspensions. Such suspensions may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents such as, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents which may be a naturally occurring phosphatide such as lecithin, a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate, a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadeca-ethyleneoxycetanol, a condensation product of ethylene oxide with a partial ester derived form a fatty acid and a hexitol such as polyoxyethylene sorbitol monooleate, or a condensation product of an ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Diluents and solvents that may be employed are, for example, water, Ringer's solution, isotonic sodium chloride solutions and isotonic glucose solutions. In addition, sterile fixed oils are conventionally employed as solvents or suspending media.

For this purpose, any bland, fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can be used in the preparation of injectables.

A composition of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritation excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are, for example, cocoa butter and polyethylene glycol.

Another formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art (see, e.g., US Patent No. 5,023,252, issued June 11, 1991, incorporated herein by reference). Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Controlled release formulations for parenteral administration include liposomal, polymeric microsphere and polymeric gel formulations that are known in the art.

It may be desirable or necessary to introduce the pharmaceutical composition to the patient via a mechanical delivery device. The construction and use of mechanical delivery devices for the delivery of pharmaceutical agents is well known in the art. Direct techniques for, for example, administering a drug directly to the brain usually involve placement of a drug delivery catheter into the patient's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of agents to specific

anatomical regions of the body, is described in US Patent No. 5,011,472, issued April 30, 1991.

The compositions of the invention can also contain other conventional pharmaceutically acceptable compounding ingredients, generally referred to as carriers or diluents, as necessary or desired. Conventional procedures for preparing such compositions in appropriate dosage forms can be utilized. Such ingredients and procedures include those described in the following references, each of which is incorporated herein by reference: Powell, M.F. *et al*, "Compendium of Excipients for Parenteral Formulations" *PDA Journal of Pharmaceutical Science & Technology* 1998, 52(5), 238-311; Strickley, R.G "Parenteral Formulations of Small Molecule Therapeutics Marketed in the United States (1999)-Part-1" *PDA Journal of Pharmaceutical Science & Technology* 1999, 53(6), 324-349; and Nema, S. *et al*, "Excipients and Their Use in Injectable Products" *PDA Journal of Pharmaceutical Science & Technology* 1997, 51(4), 166-171.

Commonly used pharmaceutical ingredients that can be used as appropriate to formulate the composition for its intended route of administration include:

**acidifying agents** (examples include but are not limited to acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid);

**alkalinizing agents** (examples include but are not limited to ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine, trolamine);

**adsorbents** (examples include but are not limited to powdered cellulose and activated charcoal);

**aerosol propellants** (examples include but are not limited to carbon dioxide, $CCl_2F_2$, $F_2ClC\text{-}CClF_2$ and $CClF_3$)

**air displacement agents** (examples include but are not limited to nitrogen and argon);

**antifungal preservatives** (examples include but are not limited to benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate);

**antimicrobial preservatives** (examples include but are not limited to benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal);

**antioxidants** (examples include but are not limited to ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite);

**binding materials** (examples include but are not limited to block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones, polysiloxanes and styrene-butadiene copolymers);

**buffering agents** (examples include but are not limited to potassium metaphosphate, dipotassium phosphate, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate)

**carrying agents** (examples include but are not limited to acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup,

syrup, corn oil, mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for injection)

**chelating agents** (examples include but are not limited to edetate disodium and edetic acid)

**colorants** (examples include but are not limited to FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel and ferric oxide red);

**clarifying agents** (examples include but are not limited to bentonite);

**emulsifying agents** (examples include but are not limited to acacia, cetomacrogol, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan monooleate, polyoxyethylene 50 monostearate);

**encapsulating agents** (examples include but are not limited to gelatin and cellulose acetate phthalate)

**flavorants** (examples include but are not limited to anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin);

**humectants** (examples include but are not limited to glycerol, propylene glycol and sorbitol);

**levigating agents** (examples include but are not limited to mineral oil and glycerin);

**oils** (examples include but are not limited to arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil);

**ointment bases** (examples include but are not limited to lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment);

**penetration enhancers (transdermal delivery)** (examples include but are not limited to monohydroxy or polyhydroxy alcohols, mono-or polyvalent alcohols, saturated or unsaturated fatty alcohols, saturated or unsaturated fatty esters, saturated or unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas)

**plasticizers** (examples include but are not limited to diethyl phthalate and glycerol);

**solvents** (examples include but are not limited to ethanol, corn oil, cottonseed oil, glycerol, isopropanol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for irrigation);

**stiffening agents** (examples include but are not limited to cetyl alcohol, cetyl esters wax, microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax);

**suppository bases** (examples include but are not limited to cocoa butter and polyethylene glycols (mixtures));

**surfactants** (examples include but are not limited to benzalkonium chloride, nonoxynol 10, oxtoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan mono-palmitate);

**suspending agents** (examples include but are not limited to agar, bentonite, carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum);

**sweetening agents** (examples include but are not limited to aspartame, dextrose, glycerol, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose);

**tablet anti-adherents** (examples include but are not limited to magnesium stearate and talc);

**tablet binders** (examples include but are not limited to acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid glucose, methylcellulose, non-crosslinked polyvinyl pyrrolidone, and pregelatinized starch);

**tablet and capsule diluents** (examples include but are not limited to dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sodium carbonate, sodium phosphate, sorbitol and starch);

**tablet coating agents** (examples include but are not limited to liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, cellulose acetate phthalate and shellac);

**tablet direct compression excipients** (examples include but are not limited to dibasic calcium phosphate);

**tablet disintegrants** (examples include but are not limited to alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, cross-linked polyvinylpyrrolidone, sodium alginate, sodium starch glycollate and starch);

**tablet glidants** (examples include but are not limited to colloidal silica, corn starch and talc);

**tablet lubricants** (examples include but are not limited to calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate);

**tablet/capsule opaquants** (examples include but are not limited to titanium dioxide);

**tablet polishing agents** (examples include but are not limited to carnuba wax and white wax);

**thickening agents** (examples include but are not limited to beeswax, cetyl alcohol and paraffin);

**tonicity agents** (examples include but are not limited to dextrose and sodium chloride);

**viscosity increasing agents** (examples include but are not limited to alginic acid, bentonite, carbomers, carboxymethylcellulose sodium, methylcellulose, polyvinyl pyrrolidone, sodium alginate and tragacanth); and

**wetting agents** (examples include but are not limited to heptadecaethylene oxycetanol, lecithins, sorbitol monooleate, polyoxyethylene sorbitol monooleate, and polyoxyethylene stearate).

Pharmaceutical compositions according to the present invention can be illustrated as follows:

**Sterile IV Solution**: A 5 mg/mL solution of the desired compound of this invention can be made using sterile, injectable water, and the pH is adjusted if necessary. The solution is diluted for administration to 1 - 2 mg/mL with sterile 5% dextrose and is administered as an IV infusion over about 60 minutes.

**Lyophilized powder for IV administration**: A sterile preparation can be prepared with (i) 100 - 1000 mg of the desired compound of this invention as a lypholized powder, (ii) 32- 327 mg/mL sodium citrate, and (iii) 300 - 3000 mg Dextran 40. The formulation is reconstituted with sterile, injectable saline or dextrose 5% to a concentration of 10 to 20 mg/mL, which is further diluted with saline or dextrose 5% to 0.2 - 0.4 mg/mL, and is administered either IV bolus or by IV infusion over 15 - 60 minutes.

**Intramuscular suspension**: The following solution or suspension can be prepared, for intramuscular injection:

50 mg/mL of the desired, water-insoluble compound of this invention
5 mg/mL sodium carboxymethylcellulose
4 mg/mL TWEEN 80
9 mg/mL sodium chloride
9 mg/mL benzyl alcohol

**Hard Shell Capsules:** A large number of unit capsules are prepared by filling standard two-piece hard galantine capsules each with 100 mg of powdered active ingredient, 150 mg of lactose, 50 mg of cellulose and 6 mg of magnesium stearate.

**Soft Gelatin Capsules:** A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into molten gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules are washed and dried. The active ingredient can be dissolved in a mixture of polyethylene glycol, glycerin and sorbitol to prepare a water miscible medicine mix.

**Tablets:** A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 mg of active ingredient, 0.2 mg. of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg. of starch, and 98.8 mg of lactose. Appropriate aqueous and non-aqueous coatings may be applied to increase palatability, improve elegance and stability or delay absorption.

**Immediate Release Tablets/Capsules:** These are solid oral dosage forms made by conventional and novel processes. These units are taken orally without water for immediate dissolution and delivery of the medication. The active ingredient is mixed in a liquid containing ingredient such as sugar, gelatin, pectin and sweeteners. These liquids are solidified into solid tablets or caplets by freeze drying and solid state extraction techniques. The drug compounds may be compressed with viscoelastic and thermoelastic sugars and polymers or effervescent components to produce porous matrices intended for immediate release, without the need of water.

The combinations of the present invention may be used for the treatment or prophylaxis of diseases of uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, or diseases which are accompanied with uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, particularly in which the uncontrolled cell growth, proliferation and/or survival,

inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, such as, for example, haematological tumours, solid tumours, and/or metastases thereof, *e.g.* leukaemias and myelodysplastic syndrome, malignant lymphomas, head and neck tumours including brain tumours and brain metastases, tumours of the thorax including non-small cell and small cell lung tumours, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof.

The term "inappropriate" within the context of the present invention, in particular in the context of "inappropriate cellular immune responses, or inappropriate cellular inflammatory responses", as used herein, is to be understood as preferably meaning a response which is less than, or greater than normal, and which is associated with, responsible for, or results in, the pathology of said diseases.

Combinations of the present invention might be utilized to inhibit, block, reduce, decrease, etc., cell proliferation and/or cell division, and/or produce apoptosis.

This method comprises administering to a mammal in need thereof, including a human, an amount of a compound A and an amount of compound B of this invention, or a pharmaceutically acceptable salt, isomer, polymorph, metabolite, hydrate, solvate or ester thereof ; etc. which is effective to treat the disorder. Hyper-proliferative disorders include but are not limited, e.g., psoriasis, keloids, and other hyperplasias affecting the skin, benign prostate hyperplasia (BPH), solid tumors, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases. Those disorders also include lymphomas, sarcomas, and leukemias.

Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, and lobular carcinoma in situ.

Examples of cancers of the respiratory tract include, but are not limited to small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

Examples of brain cancers include, but are not limited to brain stem and hypophtalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumor.

Tumors of the male reproductive organs include, but are not limited to prostate and testicular cancer. Tumors of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

Tumors of the digestive tract include, but are not limited to anal, colon, colorectal, esophageal, gallbladder, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers.

Tumors of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, urethral and human papillary renal cancers.

Eye cancers include, but are not limited to intraocular melanoma and retinoblastoma.

Examples of liver cancers include, but are not limited to hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

Skin cancers include, but are not limited to squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

Head-and-neck cancers include, but are not limited to laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancer, lip and oral cavity cancer and squamous cell. Lymphomas include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Burkitt lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

Sarcomas include, but are not limited to sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma.

Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

These disorders have been well characterized in humans, but also exist with a similar etiology in other mammals, and can be treated by administering pharmaceutical compositions of the present invention.

The term "treating" or "treatment" as stated throughout this document is used conventionally, *e.g.*, the management or care of a subject for the purpose of combating, alleviating, reducing, relieving, improving the condition of, *etc.*, of a disease or disorder, such as a carcinoma.

Combinations of the present invention might be used for the treatment of disorders associated with aberrant mitogen extracellular kinase activity, including, but not limited to stroke, heart failure, hepatomegaly, cardiomegaly, diabetes, Alzheimer's disease, cystic fibrosis, symptoms of xenograft rejections, septic shock or asthma.

The phrase "aberrant kinase activity" or "aberrant tyrosine kinase activity," includes any abnormal expression or activity of the gene encoding the kinase or of the polypeptide it encodes. Examples of such aberrant activity, include, but are not limited to, over-expression of the gene or polypeptide ; gene amplification ; mutations which produce constitutively-active or hyperactive kinase activity ; gene mutations, deletions, substitutions, additions, etc.

The present invention also provides for methods of inhibiting a kinase activity, especially of mitogen extracellular kinase, comprising administering an effective amount of a combination of the present invention, including salts, polymorphs, metabolites, hydrates, solvates, prodrugs (*e.g.*: esters) thereof, and diastereoisomeric forms thereof. Kinase activity can be inhibited in cells (*e.g., in vitro*), or in the cells of a mammalian subject, especially a human patient in need of treatment.

Combinations of the present invention might also be used for treating disorders and diseases associated with excessive and/or abnormal angiogenesis.

Inappropriate and ectopic expression of angiogenesis can be deleterious to an organism. A number of pathological conditions are associated with the growth of extraneous blood vessels. These include, e.g., diabetic retinopathy, ischemic retinal-vein occlusion, and retinopathy of prematurity [Aiello et al. New Engl. J. Med. **1994**, 331, 1480 ; Peer et al. Lab. Invest. **1995**, 72, 638], age-related macular degeneration [AMD ; see, Lopez et al. Invest. Opththalmol. Vis. Sci. **1996**, 37, 855], neovascular glaucoma, psoriasis, retrolental fibroplasias, angiofibroma, inflammation, rheumatoid arthritis (RA), restenosis, in-stent restenosis, vascular graft restenosis, etc. In addition, the increased blood supply associated with cancerous and neoplastic tissue, encourages growth, leading to rapid tumor enlargement and metastasis. Moreover, the growth of new blood and lymph vessels in a tumor provides an escape route for renegade cells, encouraging metastasis and the consequence

spread of the cancer. Thus, combinations of the present invention can be utilized to treat and/or prevent any of the aforementioned angiogenesis disorders, e.g., by inhibiting and/or reducing blood vessel formation ; by inhibiting, blocking, reducing, decreasing, etc. endothelial cell proliferation or other types involved in angiogenesis, as well as causing cell death or apoptosis of such cell types.

**Dose and administration**

Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of hyper-proliferative disorders and angiogenic disorders, by standard toxicity tests and by standard pharmacological assays for the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of the compounds of this invention can readily be determined for treatment of each desired indication. The amount of the active ingredients to be administered in the treatment of one of these conditions can vary widely according to such considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.

The total amount of the active ingredients to be administered will generally range from about 0.001 mg/kg to about 200 mg/kg body weight per day, and preferably from about 0.01 mg/kg to about 20 mg/kg body weight per day. Clinically useful dosing schedules of a compound will range from one to three times a day dosing to once every four weeks dosing. In addition, "drug holidays" in which a patient is not dosed with a drug for a certain period of time, may be beneficial to the overall balance between pharmacological effect and tolerability. A unit dosage may contain from about 0.5 mg to about 1500 mg of active ingredient, and can be administered one or more times per

day or less than once a day. The average daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily rectal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The average daily inhalation dosage regimen will preferably be from 0.01 to 100 mg/kg of total body weight.

Of course the specific initial and continuing dosage regimen for each patient will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the specific compounds employed, the age and general condition of the patient, time of administration, route of administration, rate of excretion of the drug, drug combinations, and the like. The desired mode of treatment and number of doses of a compound of the present invention or a pharmaceutically acceptable salt or ester or composition thereof can be ascertained by those skilled in the art using conventional treatment tests.

The combinations of the present invention can be used in particular in therapy and prevention, i.e. prophylaxis, of tumour growth and metastases, especially in solid tumours of all indications and stages with or without pre-treatment of the tumour growth.

Methods of testing for a particular pharmacological or pharmaceutical property are well known to persons skilled in the art.

The combinations of component A and component B of this invention can be administered as the sole pharmaceutical agent or in combination with one or more further pharmaceutical agents where the resulting combination of components A, B and C causes no unacceptable adverse effects. For example, the combinations of components A and B of this invention can be combined with component C, *i.e.* one or more further pharmaceutical agents, such as known anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agents, and the like, as well as with admixtures and combinations thereof.

Component C, can be one or more pharmaceutical agents such as aldesleukin, alendronic acid, alfaferone, alitretinoin, allopurinol, aloprim, aloxi, altretamine, aminoglutethimide, amifostine, amrubicin, amsacrine, anastrozole, anzmet, aranesp, arglabin, arsenic trioxide, aromasin, 5-azacytidine, azathioprine, BCG or tice BCG, bestatin, betamethasone acetate, betamethasone sodium phosphate, bexarotene, bleomycin sulfate, broxuridine, bortezomib, busulfan, calcitonin, campath, capecitabine, carboplatin, casodex, cefesone, celmoleukin, cerubidine, chlorambucil, cisplatin, cladribine, cladribine, clodronic acid, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, DaunoXome, decadron, decadron phosphate, delestrogen, denileukin diftitox, depo-medrol, deslorelin, dexomethasone, dexrazoxane, diethylstilbestrol, diflucan, docetaxel, doxifluridine, doxorubicin, dronabinol, DW-166HC, eligard, elitek, ellence, emend, epirubicin, epoetin alfa, epogen, eptaplatin, ergamisol, estrace, estradiol, estramustine phosphate sodium, ethinyl estradiol, ethyol, etidronic acid, etopophos, etoposide, fadrozole, farston, filgrastim, finasteride, fligrastim, floxuridine, fluconazole, fludarabine, 5-fluorodeoxyuridine monophosphate, 5-fluorouracil (5-FU), fluoxymesterone, flutamide, formestane, fosteabine, fotemustine, fulvestrant, gammagard, gemcitabine, gemtuzumab, gleevec, gliadel, goserelin, granisetron HCl, histrelin, hycamtin,

hydrocortone, eyrthro-hydroxynonyladenine, hydroxyurea, ibritumomab tiuxetan, idarubicin, ifosfamide, interferon alpha, interferon-alpha 2, interferon alfa-2A, interferon alfa-2B, interferon alfa-n1, interferon alfa-n3, interferon beta, interferon gamma-1a, interleukin-2, intron A, iressa, irinotecan, kytril, lentinan sulphate, letrozole, leucovorin, leuprolide, leuprolide acetate, lenalidomide, levamisole, levofolinic acid calcium salt, levothroid, levoxyl, lomustine, lonidamine, marinol, mechlorethamine, mecobalamin, medroxyprogesterone acetate, megestrol acetate, melphalan, menest, 6-mercaptopurine, Mesna, methotrexate, metvix, miltefosine, minocycline, mitomycin C, mitotane, mitoxantrone, Modrenal, Myocet, nedaplatin, neulasta, neumega, neupogen, nilutamide, nolvadex, NSC-631570, OCT-43, octreotide, ondansetron HCl, orapred, oxaliplatin, paclitaxel (when component B is not itself paclitaxel), pediapred, pegaspargase, Pegasys, pentostatin, picibanil, pilocarpine HCl, pirarubicin, plicamycin, porfimer sodium, prednimustine, prednisolone, prednisone, premarin, procarbazine, procrit, raltitrexed, rebif, rhenium-186 etidronate, rituximab, roferon-A, romurtide, salagen, sandostatin, sargramostim, semustine, sizofiran, sobuzoxane, solu-medrol, sparfosic acid, stem-cell therapy, streptozocin, strontium-89 chloride, synthroid, tamoxifen, tamsulosin, tasonermin, tastolactone, taxotere, teceleukin, temozolomide, teniposide, testosterone propionate, testred, thioguanine, thiotepa, thyrotropin, tiludronic acid, topotecan, toremifene, tositumomab, trastuzumab, treosulfan, tretinoin, trexall, trimethylmelamine, trimetrexate, triptorelin acetate, triptorelin pamoate, UFT, uridine, valrubicin, vesnarinone, vinblastine, vincristine, vindesine, vinorelbine, virulizin, zinecard, zinostatin stimalamer, zofran, ABI-007, acolbifene, actimmune, affinitak, aminopterin, arzoxifene, asoprisnil, atamestane, atrasentan, BAY 43-9006 (sorafenib), avastin, CCI-779, CDC-501, celebrex, cetuximab, crisnatol, cyproterone acetate, decitabine, DN-101, doxorubicin-MTC, dSLIM, dutasteride, edotecarin, eflornithine, exatecan, fenretinide, histamine dihydrochloride, histrelin hydrogel implant, holmium-166 DOTMP, ibandronic acid, interferon gamma, intron-PEG, ixabepilone,

keyhole limpet hemocyanin, L-651582, lanreotide, lasofoxifene, libra, lonafarnib, miproxifene, minodronate, MS-209, liposomal MTP-PE, MX-6, nafarelin, nemorubicin, neovastat, nolatrexed, oblimersen, onco-TCS, osidem, paclitaxel polyglutamate, pamidronate disodium, PN-401, QS-21, quazepam, R-1549, raloxifene, ranpirnase, 13-cis -retinoic acid, satraplatin, seocalcitol, T-138067, tarceva, taxoprexin, thalidomide, thymosin alpha 1, tiazofurine, tipifarnib, tirapazamine, TLK-286, toremifene, TransMID-107R, valspodar, vapreotide, vatalanib, verteporfin, vinflunine, Z-100, zoledronic acid or combinations thereof.

Alternatively, said component C can be one or more further pharmaceutical agents selected from gemcitabine, paclitaxel, cisplatin, carboplatin, sodium butyrate, 5-FU, doxirubicin, tamoxifen, etoposide, trastumazab, gefitinib, intron A, rapamycin, 17-AAG, U0126, insulin, an insulin derivative, a PPAR ligand, a sulfonylurea drug, an α-glucosidase inhibitor, a biguanide, a PTP-1B inhibitor, a DPP-IV inhibitor, a 11-beta-HSD inhibitor, GLP-1, a GLP-1 derivative, GIP, a GIP derivative, PACAP, a PACAP derivative, secretin or a secretin derivative.

Optional anti-hyper-proliferative agents which can be added as component C to the combination of components A and B of the present invention include but are not limited to compounds listed on the cancer chemotherapy drug regimens in the 11$^{th}$ Edition of the *Merck Index*, (1996), which is hereby incorporated by reference, such as asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, and vindesine.

Other anti-hyper-proliferative agents suitable for use as component C with the combination of components A and B of the present invention include but are not limited to those compounds acknowledged to be used in the treatment of neoplastic diseases in *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Ninth Edition), editor Molinoff et al., publ. by McGraw-Hill, pages 1225-1287, (1996), which is hereby incorporated by reference, such as aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2',2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyl adenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel (when component B is not itself paclitaxel), pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine.

Other anti-hyper-proliferative agents suitable for use as component C with the combination of components A and B of the present invention include but are not limited to other anti-cancer agents such as epothilone and its derivatives, irinotecan, raloxifen and topotecan.

Generally, the use of cytotoxic and/or cytostatic agents as component C in combination with a combination of components A and B of the present invention will serve to:

(1) yield better efficacy in reducing the growth of a tumor or even eliminate the tumor as compared to administration of either agent alone,

(2) provide for the administration of lesser amounts of the administered chemotherapeutic agents,

(3) provide for a chemotherapeutic treatment that is well tolerated in the patient with fewer deleterious pharmacological complications than observed with single agent chemotherapies and certain other combined therapies,

(4) provide for treating a broader spectrum of different cancer types in mammals, especially humans,

(5) provide for a higher response rate among treated patients,

(6) provide for a longer survival time among treated patients compared to standard chemotherapy treatments,

(8) provide a longer time for tumor progression, and/or

(9) yield efficacy and tolerability results at least as good as those of the agents used alone, compared to known instances where other cancer agent combinations produce antagonistic effects.

Further, the present invention relates to the use of the ratio of pro-apoptotic and anti-apoptotic proteins from the Bcl-2 family in a biological sample as a biomarker for a Mps-1 kinase inhibitor treatment.

The ratio of pro- and anti-apoptotic proteins from the Bcl-2 family in a biological sample may constitute a potential biomarker to predict the cytotoxic potential of Mps-1 kinase inhibitors.

In case of two comparable biological samples of two different organisms, the probability of success of a monotherapy with an Mps-1 kinase inhibitor is expected to be higher in the case of the organism showing the higher ratio of pro- and anti-apoptotic proteins from the Bcl-2 family.

As opposed to this, the probability of success of a combination therapy with an Mps-1 kinase inhibitor and an inhibitor of anti-apoptotic proteins from the Bcl-2 family is expected to be higher in case of the organism showing a lower ratio of pro- and anti-apoptotic proteins from the Bcl-2 family.

## EXPERIMENTAL SECTION

The following Table lists the abbreviations used in this paragraph, and in the examples section.

| Abbreviation | Meaning |
|---|---|
| EDC | 1-Ethyl-3-(3-dimethyllaminopropyl)carbodiimide |
| DCM | dichloromethane |
| DIPEA | N,N-diisopropylethylamine |
| DMF | N,N-Dimethylformamide |
| DMSO | Dimethyl sulfoxide |
| $Pd(dppf)Cl_2$ | Dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) |
| $P(oTol)_3$ | tri-o-tolylphosphine |
| NMR | nuclear magnetic resonance spectroscopy |
| rt | Room temperature |
| RT | Retention time in minutes |
| MW | molecular weight |
| NMP | *N*-methylpyrrolidinone |
| Oxone | Potassium peroxymonosulfate |
| UPLC | ultra performance liquid chromatography |

**Synthesis of compounds A of general formula (I) of the present invention**

Compounds A of general formula (I) as defined and described herein can be prepared according to the preparation methods disclosed in e.g. WO 2012/032031A1, WO 2011/013729A1, PCT/EP2013/054841 and EP13157453.5 which are incorporated by reference.

**Examples: Synthesis of compounds A of the present invention**

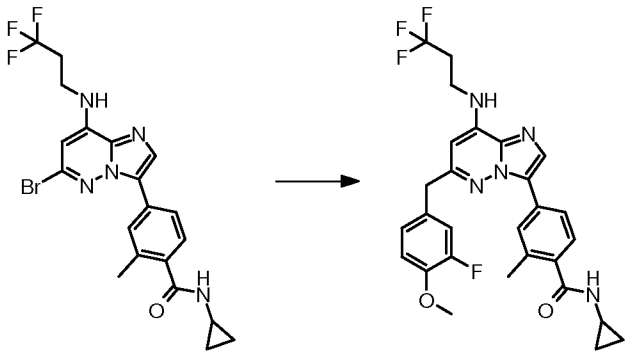
If not indicated otherwise: Analytical UPLC-MS was performed as follows: Method A: System: UPLC Acquity (Waters) with PDA Detector und Waters ZQ mass spectrometer; Column: Acquity BEH C18 1.7µm 2.1x50mm; Temperature: 60°C; Solvent A: Water + 0.1% formic acid; Solvent B: acetonitrile; Gradient: 99 % A → 1 % A (1.6 min) → 1 % A (0.4 min) ; Flow: 0.8 mL/min; Injection Volume: 1.0 µl (0.1mg-1mg/mL sample concentration); Detection: PDA scan range 210-400 nm - Fixed and ESI (+),scan range 170-800 m/z

General:

All reactions were run under an atmosphere of argon in degassed solvents unless stated otherwise.

**Example 0.1:**

***N*-Cyclopropyl-4-{6-(3-fluoro-4-methoxybenzyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide**

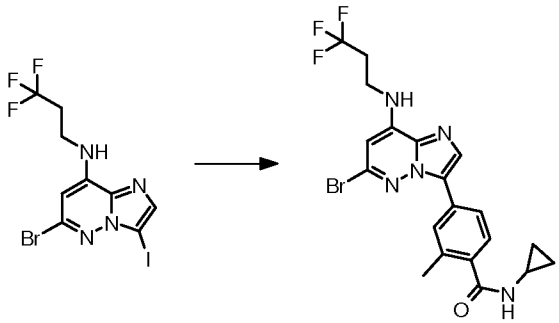


A mixture comprising 300 mg (622 µmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-*N*-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 0.1a, 2.0 mL tetrahydrofuran, 8.29 mL bromo(3-fluoro-4-methoxybenzyl)magnesium (0.75 M in tetrahydrofuran) was stirred at 23°C overnight. Stirring was continued at 50°C for 5 hours, the mixture poured into a saturated aqueous ammonium chloride solution. Water was added and the mixture extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. After filtration and removal of the solvent, the residue was purified by chromatography to give 261 mg (77%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): δ= 0.50 (2H), 0.65 (2H), 2.32 (3H), 2.56-2.72 (2H), 2.80 (1H), 3.53 (2H), 3.76 (3H), 3.96 (2H), 6.20 (1H), 7.04-7.12 (2H), 7.20 (1H), 7.30 (1H), 7.46 (1H), 7.92-7.98 (3H), 8.27 (1H) ppm.

Intermediate Example 0.1a

4-{6-Bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-*N*-cyclopropyl-2-methylbenzamide

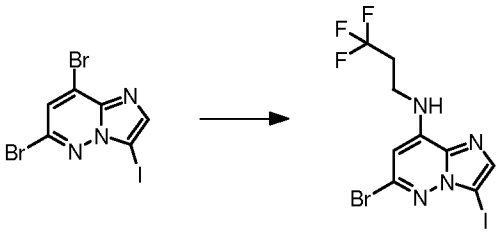


A mixture comprising 1.00 g (2.3 mmol) 6-bromo-3-iodo-*N*-(3,3,3-trifluoropropyl)imidazo[1,2-*b*]pyridazin-8-amine which was prepared according to intermediate example 0.1b, 976 mg *N*-cyclopropyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide which was prepared according to intermediate example 0.1f, 564 mg (1,1,-bis(diphenylphosphino)ferrocene)-dichloropalladium (II), 3.45 mL aqueous 2M cesium carbonate solution and 15 mL tetrahydrofuran was stirred at 45°C for 12 hours. Water was added and the

mixture was extracted with ethyl acetate and methanol. The organic layer was washed with brine and dried over sodium sulfate. After filtration and removal of the solvent the residue was purified by chromatography to give 580 mg (52%) of the title compound.

Intermediate Example 0.1b

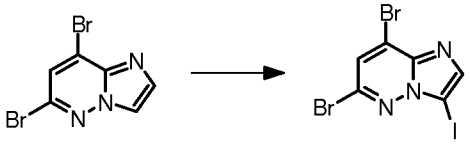
6-Bromo-3-iodo-N-(3,3,3-trifluoropropyl)imidazo[1,2-*b*]pyridazin-8-amine



To a solution of 2.30 g (5.71 mmol) 6,8-dibromo-3-iodoimidazo[1,2-*b*]pyridazine which was prepared according to intermediate example 0.1c in 40 mL *N*,*N*-dimethylformamide were added 2.0 g 3,3,3-trifluoropropan-1-amine and the mixture was stirred at 40°C overnight. Water was added and the mixture was extracted with dichloromethane and methanol. The organic phase was washed with water and dried over sodium sulfate. After filtration and removal of solvent the residue was purified by chromatography to give 2.0 g (81%) of the title compound.

Intermediate Example 0.1c

6,8-Dibromo-3-iodoimidazo[1,2-*b*]pyridazine

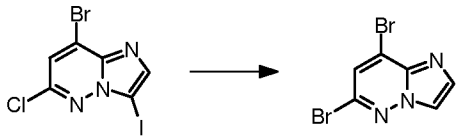


A mixture comprising 3.64 g (10.5 mmol) 6,8-dibromoimidazo[1,2-*b*]pyridazine which was prepared according to intermediate example 0.1d, 2.8 g *N*-iodosuccinimide, 72.6 mL *N*,*N*-dimethylformamide was heated at 60°C for 3 hours. 1.4 g *N*-iodosuccinimide were added and heating was continued for additional 4 hours. Most of the solvent was removed, water was added and the

mixture was extracted with dichloromethane. The organic phase was washed with water, sodium thiosulfate solution and dried over sodium sulfate. After filtration and removal of solvent the residue was purified by chromatography to give 3.64 g (86%) of the title compound.

Intermediate Example 0.1d

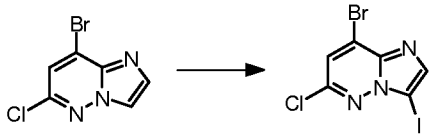
6,8-Dibromoimidazo[1,2-*b*]pyridazine



A mixture of 5.0 (14.0 mmol) 8-bromo-6-chloro-3-iodoimidazo[1,2-*b*]pyridazine which was prepared according to intermediate example 0.1e, 30 mL of hydrogen bromide solution (33% in acetic acid) was stirred at 120°C for 1 hour under microwave irradiation. The mixture was poured into water and extracted with dichloromethane. The organic phase was washed with sodium thiosulfate and sodium hydrogencarbonate solution and dried over sodium sulfate. After filtration and removal of solvent the residue was purified by chromatography to give 3.0 g (78%) of the title compound.

Intermediate Example 0.1e

8-Bromo-6-chloro-3-iodoimidazo[1,2-*b*]pyridazine

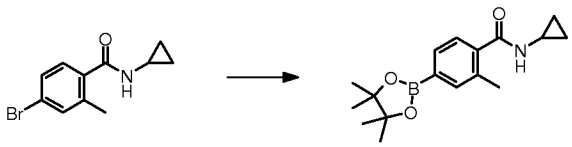


A mixture comprising 100 g (430 mmol) 8-bromo-6-chloroimidazo[1,2-*b*]pyridazine which was prepared according to a procedure described in US2007/78136 (WO2007/38314), 145 g N-iodosuccinimide, 5 percent per weight conc. hydrochloric acid and 1 L trichloromethane was heated at reflux for 6 hours. 20 g *N*-iodosuccinimide were added and heating was continued for additional 3 hours. The precipitate was removed and the filtrate was washed with 1N sodium hydroxide solution, brine and dried over sodium sulfate. After

filtration and removal of solvent diisopropyl ether was added and the residue was stirred at 23°C overnight. The precipitate was filtered off and dried to give 66.6 g (43%) of the title compound.

Intermediate Example 0.1f

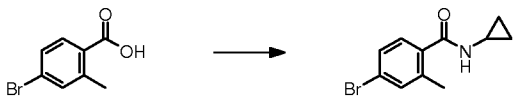
*N*-Cyclopropyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide



To a solution of 260 g (1.02 mol) 4-bromo-*N*-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 0.1g in 2 L dioxane at 23°C were added 390 g bis-(pinacolato)-diboron, 19.5 g 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, 150 g potassium acetate and 9.37 g tris-(dibenzylidenaceton)-dipalladium(0) and the mixture was refluxed for 6 h. After cooling to 23°C, water and ethyl acetate were added and the mixture stirred for 15 min. The organic phase was washed with water, dried over sodium sulfate, filtered and evaporated. The residue was purified by chromatography to give 308 g (56%) of the title compound.

Intermediate Example 0.1g

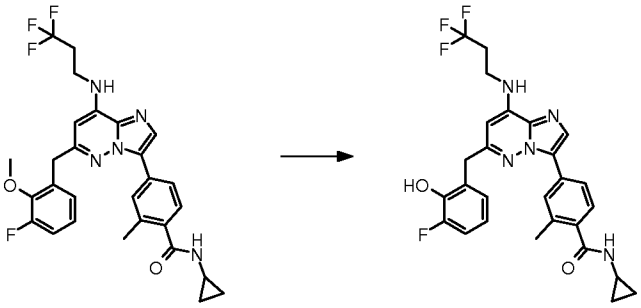
4-Bromo-*N*-cyclopropyl-2-methylbenzamide



To a stirred solution of 300 g (1.4 mol) 4-bromo-2-methylbenzoic acid in 8.4 L dichloromethane at 23°C were added 79.6 g cyclopropanamine and 320.9 g EDC. After stirring overnight, the solution was washed with water and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over sodium sulfate, filtered and evaporated. The remaining solid was triturated with diisopropyl ether, filtered, washed and dried in vacuo to yield 260 g (73%)of the title compound.

**Example 0.2:**

***N*-Cyclopropyl-4-{6-(3-fluoro-2-hydroxybenzyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide**

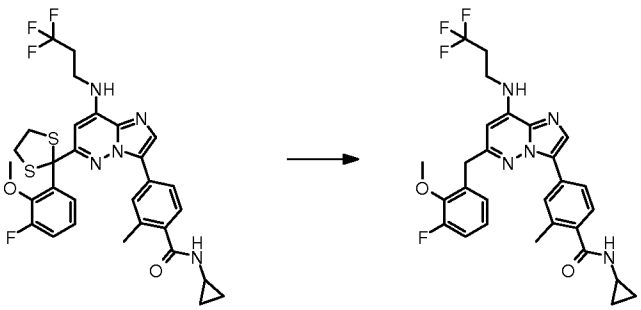


To a solution of 14.2 mg (26 µmol) *N*-cyclopropyl-4-{6-(3-fluoro-2-methoxybenzyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 0.2a in 1 mL dichloromethane were added 131 µL of a 1M boron tribromide solution in dichloromethane and the mixture was stirred at 23°C for 1 hour. Methanol was added and solvents were removed. The residue was purified by chromatography to give 4.9 mg (32%) of the title compound. UPLC-MS: RT = 1.20 min; m/z (ES+) 528.5 [$MH^+$]; required MW = 527.5.

$^1$H-NMR (DMSO-$d_6$): δ= 0.49 (2H), 0.65 (2H), 2.29 (3H), 2.56-2.70 (2H), 2.80 (1H), 3.52 (2H), 4.04 (2H), 6.15 (1H), 6.74 (1H), 6.96-7.06 (2H), 7.26 (1H), 7.41 (1H), 7.88-7.96 (3H), 8.23 (1H), 8.70 (1H) ppm.

Intermediate Example 0.2a

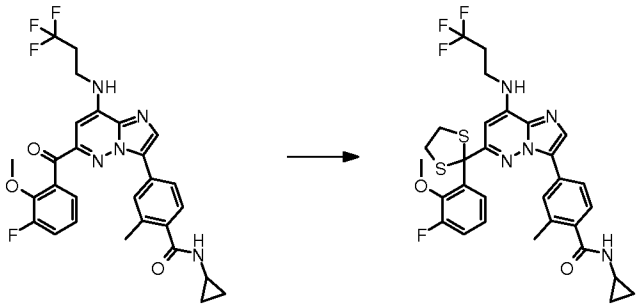
*N*-Cyclopropyl-4-{6-(3-fluoro-2-methoxybenzyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide



A mixture comprising 30 mg (48 µmol) *N*-cyclopropyl-4-{6-[2-(3-fluoro-2-methoxyphenyl)-1,3-dithiolan-2-yl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 0.2b, 800 µL methanol, 200 µL tetrahydrofuran, 18.8 mg dichloronickel hexahydrate and 15.0 mg sodium borohydride was stirred at 23°C for 2 hours. After filtration water was added and the mixture extracted with ethyl acetate. The organic layer was washed with water and dried over sodium sulfate. After filtration and removal of the solvent, 24.2 mg (93%) of the title compound were obtained that was used without further purification. UPLC-MS: RT = 1.30 min; m/z (ES+) 542.6 [$MH^+$]; required MW = 541.6.

Intermediate Example 0.2b

*N*-Cyclopropyl-4-{6-[2-(3-fluoro-2-methoxyphenyl)-1,3-dithiolan-2-yl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide



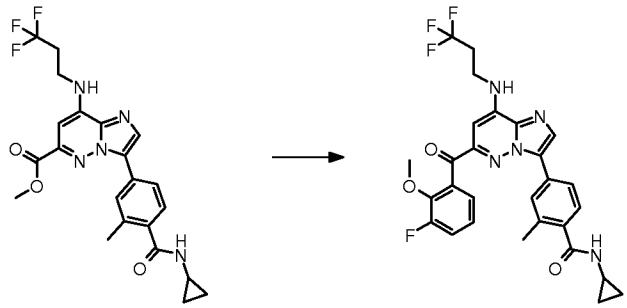
A mixture comprising 150 mg (270 µmol) *N*-cyclopropyl-4-{6-(3-fluoro-2-methoxybenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 0.2c, 340 µL ethane-1,2-dithiol and 37.5 µL boron trifluoride acetic acid complex was heated at 60°C for 16 hours. Ethyl acetate was added and the mixture washed with saturated sodium hydrogen carbonate, sodium hydroxide solution (1M) and brine. The organic layer was dried over sodium sulfate. After filtration and removal of the solvent, the residue was purified

by chromatography to give 63.0 mg (37%) of the title compound. UPLC-MS: RT = 1.37 min; m/z (ES+) 632.7 [$MH^+$]; required MW = 631.7.

$^1$H-NMR (DMSO-$d_6$): δ= 0.44-0.51 (2H), 0.59-0.68 (2H), 2.58-2.72 (3H), 2.77 (1H), 3.13 (2H), 3.32-3.40 (2H), 3.42 (3H), 3.50-3.69 (4H), 6.71 (1H), 7.06 (1H), 7.17 (1H), 7.23-7.33 (1H), 7.53-7.60 (2H), 7.69 (1H), 7.83 (1H), 8.00 (1H), 8.19 (1H) ppm.

Intermediate Example 0.2c

*N*-Cyclopropyl-4-{6-(3-fluoro-2-methoxybenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide

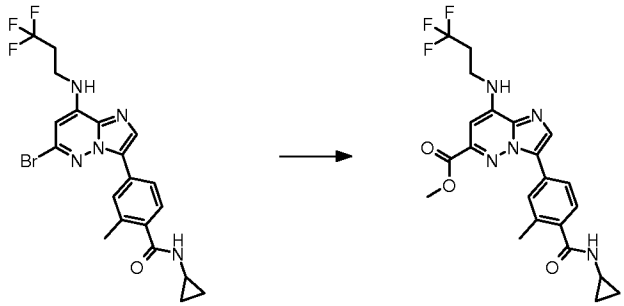


A mixture comprising 460 mg (997 mmol) methyl 3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazine-6-carboxylate which was prepared according to intermediate example 0.2d, 10 mL tetrahydrofuran and 126 mg *N*-methoxymethanamine hydrochloride was cooled to -5°C. 35.9 mL bromo(3-fluoro-2-methoxyphenyl)magnesium solution in tetrahydrofuran (0.5 M) were added, the mixture stirred at 23°C overnight and poored into cold hydrochloric acid. Ethyl acetate was added and the mixture washed with brine. The organic layer was dried over sodium sulfate. After filtration and removal of the solvent, the residue was purified by chromatography to give 306 mg (55%) of the title compound. UPLC-MS: RT = 1.30 min; m/z (ES+) 556.5 [$MH^+$]; required MW = 555.5.

$^1$H-NMR (DMSO-$d_6$): δ= 0.44-0.51 (2H), 0.59-0.70 (2H), 2.10 (3H), 2.64-2.83 (3H), 3.62 (3H), 3.72 (2H), 6.79 (1H), 7.00-7.06 (1H), 7.14 (1H), 7.26 (1H), 7.50 (1H), 7.54 (1H), 7.71 (1H), 7.82 (1H), 7.94 (1H), 8.22 (1H) ppm.

Intermediate Example 0.2d

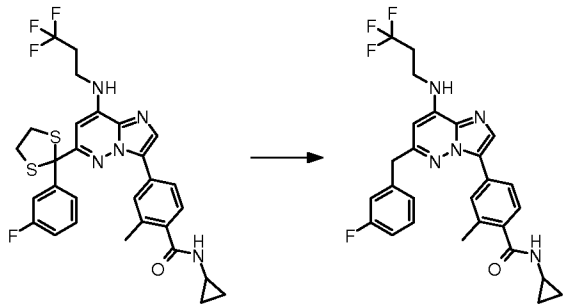
Methyl 3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazine-6-carboxylate



A mixture comprising 5.0 g (10.37 mmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-*N*-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 0.1a, 100 mL methanol, 10 mL tetrahydrofuran, 1.7 g (1,1,-bis(diphenylphosphino)ferrocene)-dichloropalladium (II), 1.6 mL triethylamine was reacted under an atmosphere of carbon monoxide at 100°C, 9-12 bar for 24 hours. After removal of the solvents, the residue was purified by chromatography to give 3.32 g (63%) of the title compound. UPLC-MS: RT = 1.11 min; m/z (ES+) 462.5 [$MH^+$]; required MW = 461.5.

**Example 0.3:**

***N*-Cyclopropyl-4-{6-(3-fluorobenzyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide**



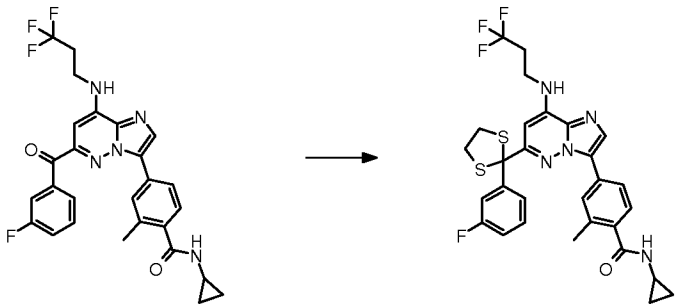
45 mg (75 µmol) *N*-cyclopropyl-4-{6-[2-(3-fluorophenyl)-1,3-dithiolan-2-yl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example

0.3a were transformed in analogy to intermediate example 0.2a to give after working up and purification 16.3 mg (42%) of the title compound. UPLC-MS: RT = 1.30 min; m/z (ES+) 556.5 [$MH^+$]; required MW = 555.5.

$^1$H-NMR (DMSO-$d_6$): δ= 0.50 (2H), 0.65 (2H), 2.32 (3H), 2.56-2.72 (2H), 2.80 (1H), 3.54 (2H), 4.05 (2H), 6.22 (1H), 7.03 (1H), 7.15-7.23 (2H), 7.26-7.38 (2H), 7.46 (1H), 7.91-7.99 (3H), 8.24 (1H) ppm.

Intermediate Example 0.3a

*N*-Cyclopropyl-4-{6-[2-(3-fluorophenyl)-1,3-dithiolan-2-yl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide

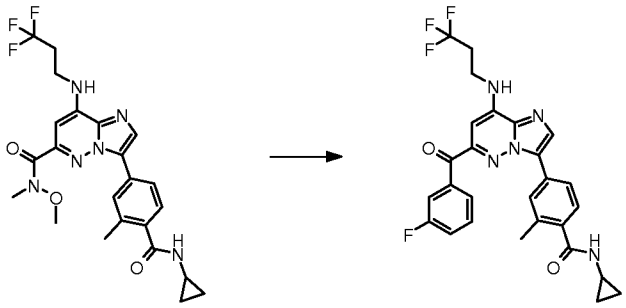


80 mg (152 µmol) *N*-cyclopropyl-4-{6-(3-fluorobenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 0.3b were transformed in analogy to intermediate example 0.2b to give after working up and purification 45 mg (49%) of the title compound. UPLC-MS: RT = 1.39 min; m/z (ES+) 602.7 [$MH^+$]; required MW = 601.7.

$^1$H-NMR (DMSO-$d_6$): δ= 0.46-0.53 (2H), 0.61-0.68 (2H), 2.30 (3H), 2.52-2.65 (2H), 2.76-2.85 (1H), 3.32-3.41 (2H), 3.48-3.62 (4H), 6.26 (1H), 7.06-7.13 (1H), 7.26 (1H), 7.34 (1H), 7.39-7.43 (1H), 7.48 (1H), 7.63 (1H), 7.91 (1H), 8.05 (2H), 8.25 (1H) ppm.

Intermediate Example 0.3b

*N*-Cyclopropyl-4-{6-(3-fluorobenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide

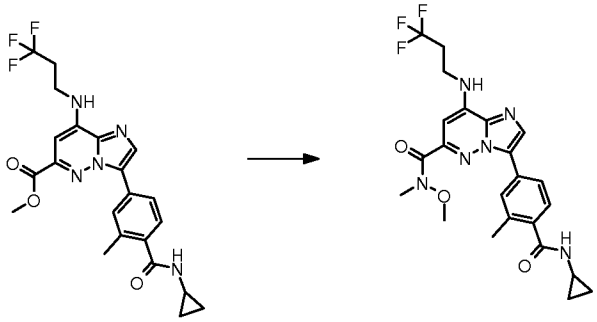


To a solution of 400 mg (0.816 mmol) 3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-*N*-methoxy-*N*-methyl-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazine-6-carboxamide which was prepared according to intermediate example 0.3c in 30 mL THF were added 12.23mL (15 eq) bromo(3-fluorophenyl)magnesium (1M solution in THF) at -20°C . After further 30 min. stirring at this temperature, the solution is added dropwise to 50 mL ice-cold 0.5 M HCl solution to give after working up and purification 334 mg (78%) of the title compound. UPLC-MS: RT = 1.32 min; m/z (ES+) 526.5 [MH+]; required MW = 525.5.

$^1$H-NMR (DMSO-$d_6$): δ= 0.44-0.52 (2H), 0.59-0.69 (2H), 2.20 (3H), 2.62-2.84 (3H), 3.70 (2H), 6.74 (1H), 7.10 (1H), 7.24 (1H), 7.51-7.66 (2H), 7.79-7.96 (4H), 8.15 (1H), 8.23 (1H) ppm.

Intermediate Example 0.3c

3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-*N*-methoxy-*N*-methyl-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazine-6-carboxamide



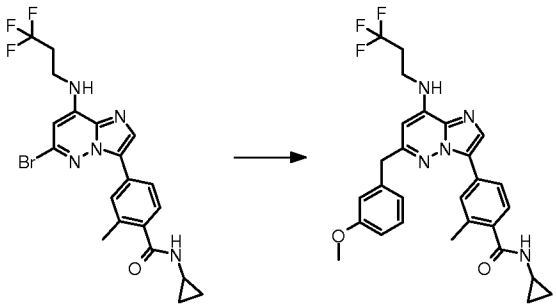
To a suspension of 6.62 g (14.34 mmol) methyl 3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazine-6-carboxylate which was prepared according to intermediate example 0.2d and

2.10 g (21.52 mmol) *N*-methoxymethanamine hydrochloride (1:1) in 30 mL THF were dropwise added 33 mL lithium chloride - chloro(propan-2-yl)magnesium (1:1) (3 eq, 1.3M solution in THF) at -20°C . After 2h stirring at this temperature, further 55 mL (5 eq) mL lithium chloride - chloro(propan-2-yl)magnesium (1:1) solution were added. After 40 min the reaction is quenched by addition of 20% ammonia chloride solution to give after working up and purification 3.8 g (55%) of the title compound. UPLC-MS: RT = 1.05 min; m/z (ES+) 491.5 [$MH^+$]; required MW = 490.5.

$^1$H-NMR (DMSO-$d_6$): δ= 0.44-0.53 (2H), 0.60-0.69 (2H), 2.35 (3H), 2.57-2.73 (2H), 2.81 (1H), 3.54-3.69 (5H), 6.36 (1H), 7.36 (1H), 7.81 (1H), 7.90 (1H), 7.95 (1H), 8.04 (1H), 8.28 (1H) ppm.

**Example 0.4:**

***N*-cyclopropyl-4-{6-(3-methoxybenzyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide**

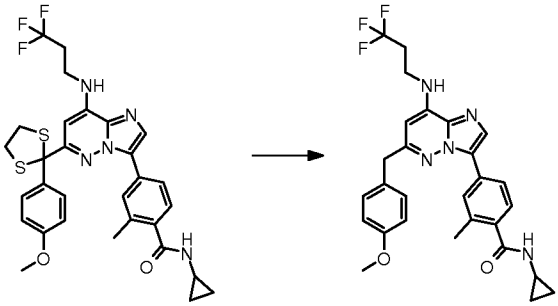


100 mg (207 µmol) 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-*N*-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 0.1a were transformed in analogy to intermediate example 0.1 using bromo(3-methoxybenzyl)magnesium to give after working up and purification 28.7 mg (25%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): δ= 0.50 (2H), 0.65 (2H), 2.33 (3H), 2.56-2.72 (2H), 2.80 (1H), 3.53 (2H), 3.69 (3H), 3.99 (2H), 6.28 (1H), 6.77 (1H), 6.87-6.97 (2H), 7.20 (1H), 7.32 (1H), 7.54 (1H), 7.93-8.05 (3H), 8.28 (1H) ppm.

**Example 0.5**

**_N_-Cyclopropyl-4-{6-(4-methoxybenzyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-_b_]pyridazin-3-yl}-2-methylbenzamide**

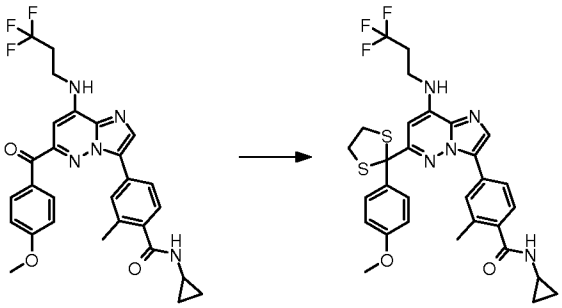


30 mg (49 µmol) _N_-cyclopropyl-4-{6-[2-(4-methoxyphenyl)-1,3-dithiolan-2-yl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-_b_]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 0.5a were transformed in analogy to intermediate example 0.2a to give after working up and purification 7.9 mg (29%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): $\delta$= 0.50 (2H), 0.65 (2H), 2.33 (3H), 2.55-2.71 (2H), 2.80 (1H), 3.52 (2H), 3.68 (3H), 3.94 (2H), 6.16 (1H), 6.85 (2H), 7.25 (2H), 7.31 (1H), 7.43 (1H), 7.91-8.01 (3H), 8.27 (1H) ppm.

Intermediate Example 0.5a

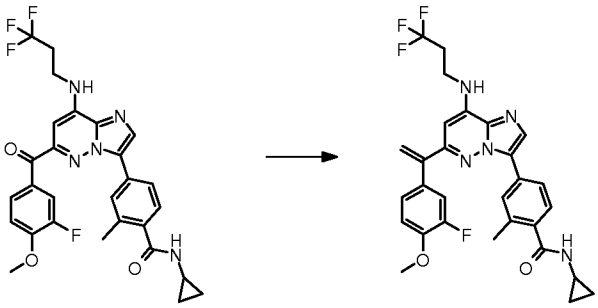
_N_-Cyclopropyl-4-{6-[2-(4-methoxyphenyl)-1,3-dithiolan-2-yl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-_b_]pyridazin-3-yl}-2-methylbenzamide



100 mg (186 µmol) _N_-cyclopropyl-4-{6-(4-methoxybenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-_b_]pyridazin-3-yl}-2-methylbenzamide which was prepared according to example 9 were transformed in analogy to intermediate example 0.2b to give after working up and purification 60.2 mg (53%) of the title compound.

**Example 1:**

***N*-Cyclopropyl-4-{6-[1-(3-fluoro-4-methoxyphenyl)ethenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide**

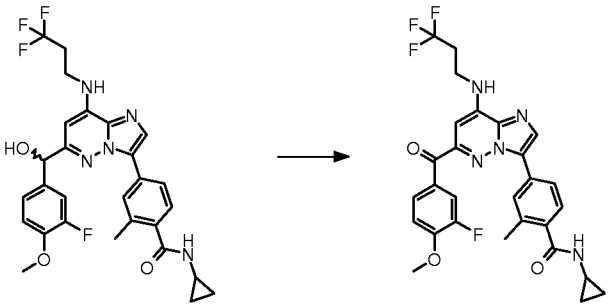


To a suspension of 386 mg methyl(triphenyl)phosphonium bromide in 6.8 mL tetrahydrofuran at -78°C were added 421 µL n-butyllithium (2.5M in hexane). After the mixture was stirred at 0°C for 0.5 hours a solution of 150 mg (270 µmol) *N*-cyclopropyl-4-{6-(3-fluoro-4-methoxybenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 1a in 3.2 mL tetrahydrofuran was added and stirring was continued overnight. Water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated ammonium chloride solution and dried over sodium sulfate. After filtration and removal of the solvent the residue was purified by chromatography to give 127 mg (81%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): δ= 0.48 (2H), 0.64 (2H), 2.17 (3H), 2.61-2.73 (2H), 2.78 (1H), 3.61 (2H), 3.84 (3H), 5.73 (1H), 5.93 (1H), 6.36 (1H), 7.13-7.23 (3H), 7.30 (1H), 7.54 (1H), 7.82 (1H), 7.88 (1H), 8.01 (1H), 8.21 (1H) ppm.

Intermediate Example 1a

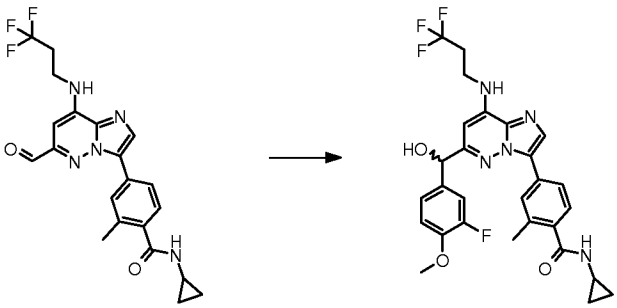
*N*-Cyclopropyl-4-{6-(3-fluoro-4-methoxybenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide



To a solution of 82 µL ethanedioyl dichloride in 2.5 mL dichloromethane were added at -78°C 133 µL dimethyl sulfoxide followed by a solution of 262 mg (470 µmol) (*RS*)-*N*-cyclopropyl-4-{6-[(3-fluoro-4-methoxyphenyl)(hydroxy)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 1b in 2.5 mL dichloromethane and 0.6 mL dimethyl sulfoxide. After 1 hour, 393 µL triethylamine were added and the mixture was stirred at 23°C for 20 minutes. Water was added and the mixture was extracted dichloromethane and methanol (9:1). The organic layer was washed with water and dried over sodium sulfate. After filtration and removal of the solvent the residue was purified by chromatography to give 210 mg (80%) of the title compound.

Intermediate Example 1b

(*RS*)-*N*-Cyclopropyl-4-{6-[(3-fluoro-4-methoxyphenyl)(hydroxy)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide

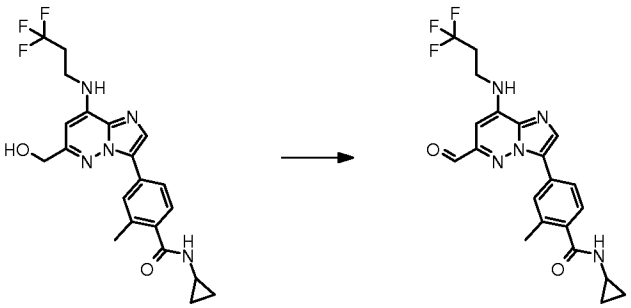


To a solution of 500 mg (1.16 mmol) *N*-cyclopropyl-4-{6-formyl-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which

was prepared according to intermediate example 1c in 20 mL tetrahydrofuran were added at 0°C a solution of bromo(3-fluoro-4-methoxyphenyl)magnesium freshly prepared from 598 µL 4-bromo-2-fluoro-1-methoxybenzene, 113 mg magnesium and 5 mL tetrahydrofuran. After 1 hour the mixture was poured into a saturated aqueous ammonium chloride solution. Water was added and the mixture extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. After filtration and removal of the solvent, the residue was purified by chromatography to give 319 mg (46%) of the title compound.

Intermediate Example 1c

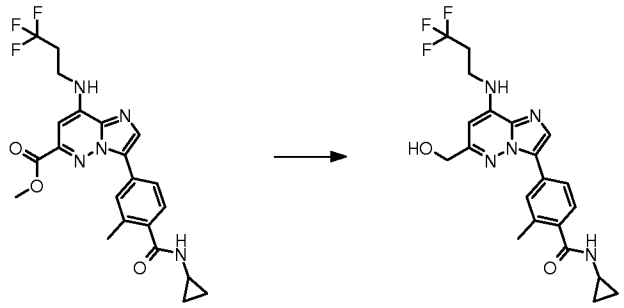
*N*-Cyclopropyl-4-{6-formyl-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide



1.60 g (3.69 mmol) *N*-cyclopropyl-4-{6-(hydroxymethyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 1d were transformed in analogy to intermediate example 1a to give after working up and purification 1.50 g (94%) of the title compound.

Intermediate Example 1d

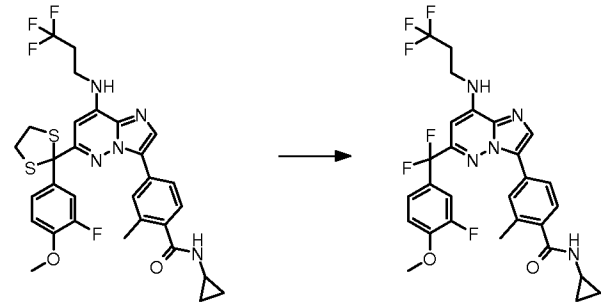
*N*-Cyclopropyl-4-{6-(hydroxymethyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide



To a solution of 2.17 g (4.70 mmol) methyl 3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazine-6-carboxylate which was prepared according to intermediate example 0.2d in 220 mL tetrahydrofuran at 0°C were added 23.5 mL diisobutylaluminiumhydrid solution (1M in tetrahydrofuran). After 1 hour the mixture was poured into a saturated aqueous ammonium chloride solution. Water was added and the mixture extracted with ethyl acetate and methanol (9:1). The organic layer was washed with brine and dried over sodium sulfate. After filtration and removal of the solvent, the residue was purified by chromatography to give 1.56 g (73%) of the title compound.

**Example 2:**

***N*-Cyclopropyl-4-{6-[difluoro(3-fluoro-4-methoxyphenyl)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide**



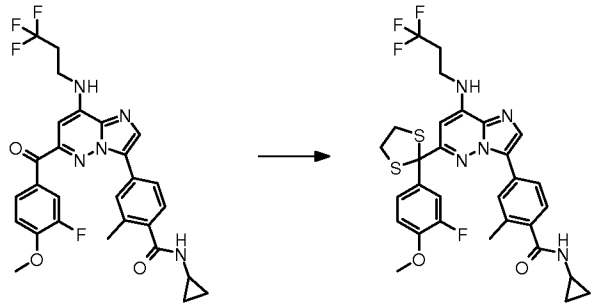
To a mixture of 32.5 mg 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane ditetrafluoroborate and 1.16 mL pyridine hydrofluoride at 0°C was added a solution of 29 mg (46 µmol) *N*-cyclopropyl-4-{6-[2-(3-fluoro-4-methoxyphenyl)-1,3-dithiolan-2-yl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which

was prepared according to intermediate example 2a in 0.5 mL dichloromethane. The mixture was stirred at 23°C overnight and poured into water. The organic layer was washed with water and brine and dried over sodium sulfate. After filtration and removal of the solvent, the residue was purified by chromatography to give 14.6 mg (52%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): δ= 0.49 (2H), 0.65 (2H), 2.23 (3H), 2.61-2.84 (3H), 3.68 (2H), 3.86 (3H), 6.58 (1H), 7.24 (1H), 7.31 (1H), 7.42 (1H), 7.50 (1H), 7.72-7.81 (2H), 7.97 (1H), 8.09 (1H), 8.27 (1H) ppm.

Intermediate Example 2a

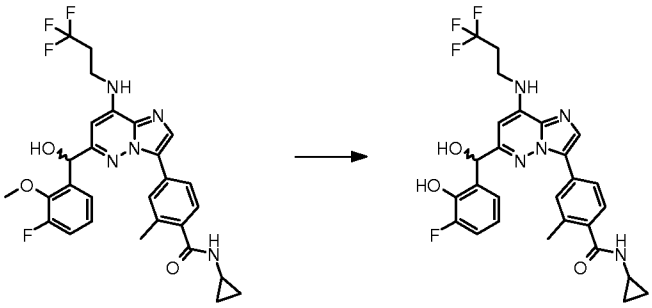
*N*-Cyclopropyl-4-{6-[2-(3-fluoro-4-methoxyphenyl)-1,3-dithiolan-2-yl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide



50 mg (90 µmol) *N*-cyclopropyl-4-{6-(3-fluoro-4-methoxybenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 1a were transformed in analogy to intermediate example 0.2b to give after working up and purification 29 mg (51%) of the title compound.

**Example 3:**

**(*RS*)-*N*-Cyclopropyl-4-{6-[(3-fluoro-2-hydroxyphenyl)(hydroxy)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide**

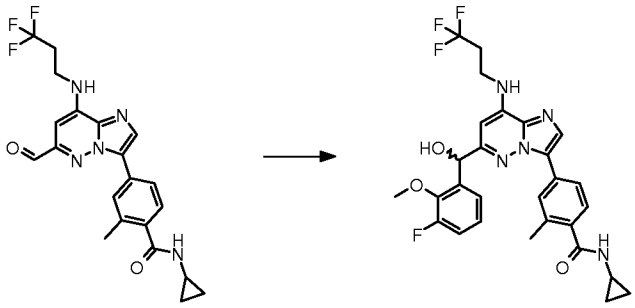


A mixture of 25.0 mg (45 µmol) (*RS*)-*N*-cyclopropyl-4-{6-[(3-fluoro-2-methoxyphenyl)(hydroxy)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 3a, 25.1 mg sodium methanethiolate and 900 µL dimethyl sulfoxide was heated under microwave irradiation for 5 minutes at 130°C. Hydrochloric acid was added and the solvent removed. The residue was purified by chromatography to give 8.2 mg (32%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): δ= 0.50 (2H), 0.65 (2H), 2.29 (3H), 2.56-2.72 (2H), 2.79 (1H), 3.57 (2H), 6.00 (1H), 6.33 (1H), 6.33 (1H), 6.79 (1H), 7.03 (1H), 7.24 (1H), 7.27 (1H), 7.44 (1H), 7.86-7.92 (2H), 8.96 (1H), 8.24 (1H) ppm.

Intermediate Example 3a

(*RS*)-*N*-Cyclopropyl-4-{6-[(3-fluoro-2-methoxyphenyl)(hydroxy)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide

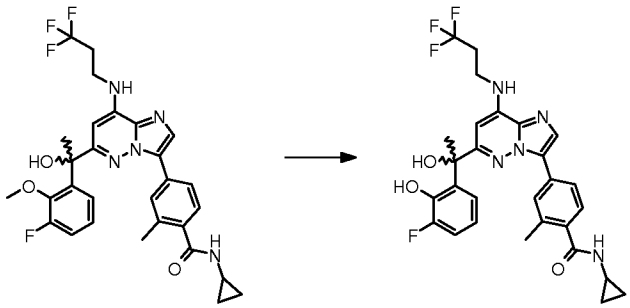


500 mg (1.16 mmol) *N*-cyclopropyl-4-{6-formyl-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 1c were transformed in analogy to intermediate example 1b using bromo(3-fluoro-2-

methoxyphenyl)magnesium to give after working up and purification 519 mg (80%) of the title compound.

**Example 4:**

**(*RS*)-*N*-Cyclopropyl-4-{6-[1-(3-fluoro-2-hydroxyphenyl)-1-hydroxyethyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide**

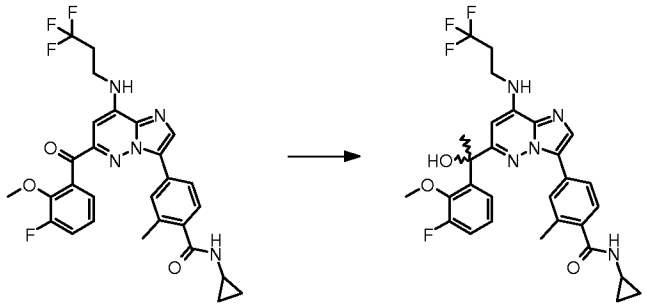


23.5 mg (41 µmol) (*RS*)-*N*-cyclopropyl-4-{6-[1-(3-fluoro-2-methoxyphenyl)-1-hydroxyethyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 4a were transformed in analogy to example 3 to give after working up and purification 9.5 mg (39%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): δ= 0.50 (2H), 0.65 (2H), 1.91 (3H), 2.32 (3H), 2.52-2.65 (2H), 2.80 (1H), 3.49 (2H), 6.22 (1H), 6.69 (1H), 7.00 (1H), 7.18 (1H), 7.28 (1H), 7.35 (1H), 7.93 (1H), 7.96-8.02 (2H), 8.25 (1H), 8.59 (1H) ppm.

Intermediate Example 4a

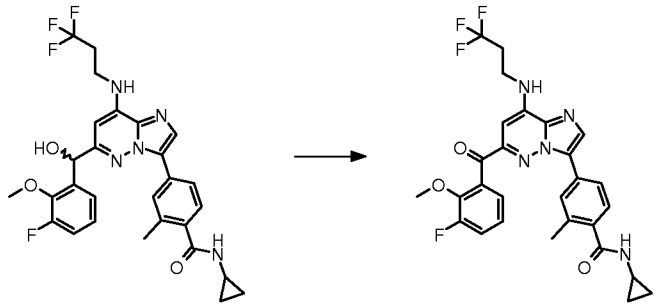
(*RS*)-*N*-Cyclopropyl-4-{6-[1-(3-fluoro-2-methoxyphenyl)-1-hydroxyethyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide



To a solution of 50 mg (90 µmol) *N*-cyclopropyl-4-{6-(3-fluoro-2-methoxybenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 4b in 2.5 mL tetrahydrofuran at -78°C were added 225 µL methyllithium (2.5M in diethyl ether). The mixture was stirred at -50°C for 30 minutes, poured into water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous ammonium chloride solution and dried over sodium sulfate. After filtration and removal of the solvent, the residue was purified by chromatography to give 29 mg (56%) of the title compound.

Intermediate Example 4b

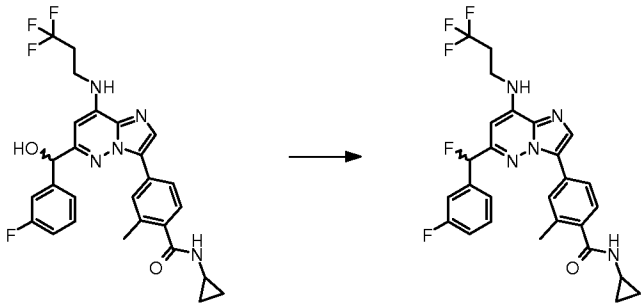
*N*-Cyclopropyl-4-{6-(3-fluoro-2-methoxybenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide



442 mg (793 µmol) (*RS*)-*N*-cyclopropyl-4-{6-[(3-fluoro-2-methoxyphenyl)(hydroxy) methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 3a were transformed in analogy to intermediate example 1a to give after working up and purification 317 mg (72%) of the title compound.

**Example 5:**

**(*RS*)-*N*-Cyclopropyl-4-{6-[fluoro(3-fluorophenyl)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide**

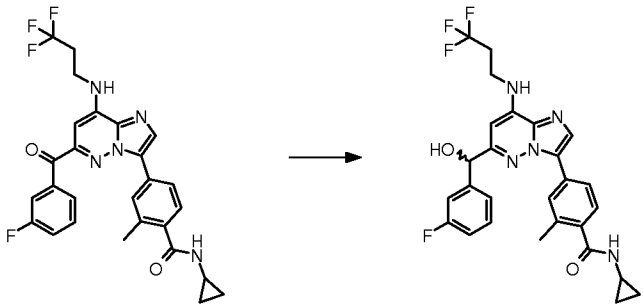


50 mg (95 µmol) (*RS*)-*N*-cyclopropyl-4-{6-[(3-fluorophenyl)(hydroxy)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 5a were transformed in analogy to example 2 to give after working up and purification 4.3 mg (7%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): δ= 0.50 (2H), 0.65 (2H), 2.31 (3H), 2.50 (1H), 2.61-2.74 (2H), 2.80 (1H), 3.63 (2H), 6.41 (1H), 6.68 (1H), 7.22 (1H), 7.29 (1H), 7.33-7.39 (1H), 7.46 (1H), 7.75 (1H), 7.87-7.90 (2H), 8.02 (1H), 8.26 (1H) ppm.

Intermediate Example 5a

(*RS*)-*N*-Cyclopropyl-4-{6-[(3-fluorophenyl)(hydroxy)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide

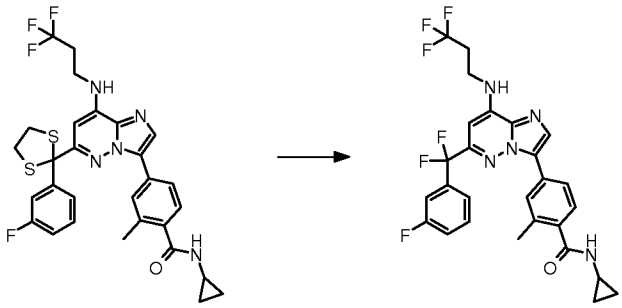


To a solution of 210 mg (400 µmol) *N*-cyclopropyl-4-{6-(3-fluorobenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 0.3b in 5 mL dichloromethane were added at 3°C 151 mg sodium borohydride and stirring was continued for 1 hour and at 23°C for 1 hour. Water was added and the the organic layer was washed with water and dried over sodium

sulfate. After filtration and removal of the solvent, 209 mg (96%) of the title compound were obtained that was used without further purification.

**Example 6:**

***N*-Cyclopropyl-4-{6-[difluoro(3-fluorophenyl)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide**

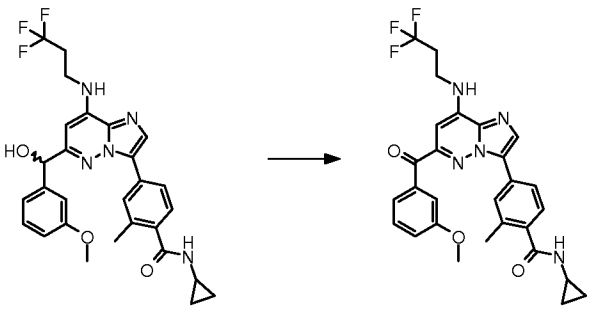


28 mg (46 µmol) *N*-cyclopropyl-4-{6-[2-(3-fluorophenyl)-1,3-dithiolan-2-yl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 0.3a were transformed in analogy to example 2 to give after working up and purification 7.9 mg (31%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): δ= 0.49 (2H), 0.65 (2H), 2.24 (3H), 2.61-2.84 (3H), 3.70 (2H), 6.61 (1H), 7.23 (1H), 7.41 (1H), 7.46-7.53 (2H), 7.57 (1H), 7.74 (1H), 7.75 (1H), 7.97 (1H), 8.09 (1H), 8.24 (1H) ppm.

**Example 7:**

***N*-Cyclopropyl-4-{6-(3-methoxybenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide**

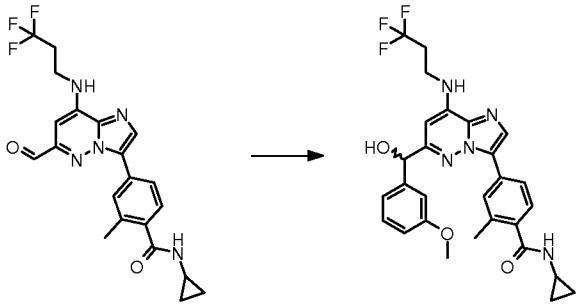


52 mg (96 µmol) (*RS*)-*N*-cyclopropyl-4-{6-[hydroxy(3-methoxyphenyl)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 7a were transformed in analogy to intermediate example 1a to give after working up and purification 34 mg (62%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): δ= 0.47 (2H), 0.64 (2H), 2.19 (3H), 2.62-2.82 (3H), 3.69 (2H), 3.76 (3H), 6.71 (1H), 7.23 (1H), 7.27 (1H), 7.48 (1H), 7.54 (1H), 7.61 (1H), 7.84 (1H), 7.89 (1H), 7.96 (1H), 8.15 (1H), 8.22 (1H) ppm.

Intermediate Example 7a

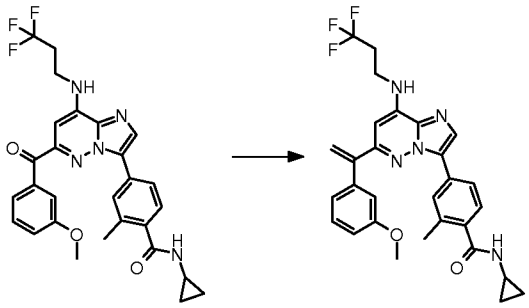
(*RS*)-*N*-cyclopropyl-4-{6-[hydroxy(3-methoxyphenyl)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide



110 mg (255 µmol) *N*-cyclopropyl-4-{6-formyl-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 1c were transformed in analogy to intermediate example 1b using bromo(3-methoxyphenyl)magnesium to give after working up and purification 79 mg (55%) of the title compound.

**Example 8:**

**_N_-Cyclopropyl-4-{6-[1-(3-methoxyphenyl)vinyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide**

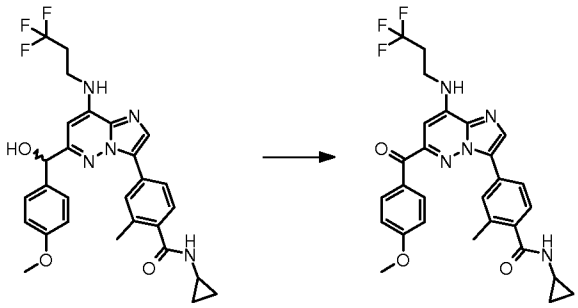


175 mg (326 µmol) *N*-cyclopropyl-4-{6-(3-methoxybenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to example 7 were transformed in analogy to example 1 to give after working up and purification 96.3 mg (55%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): $\delta$= 0.48 (2H), 0.64 (2H), 2.18 (3H), 2.60-2.72 (2H), 2.78 (1H), 3.60 (2H), 3.71 (3H), 5.75 (1H), 5.98 (1H), 6.34 (1H), 6.92-6.99 (3H), 7.21 (1H), 7.29 (1H), 7.53 (1H), 7.84 (1H), 7.89 (1H), 8.01 (1H), 8.21 (1H) ppm.

**Example 9:**

**_N_-Cyclopropyl-4-{6-(4-methoxybenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide**

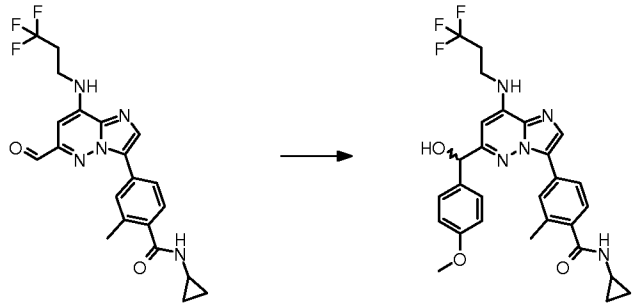


400 mg (741 µmol) (*RS*)-*N*-cyclopropyl-4-{6-[hydroxy(4-methoxyphenyl)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 9a were transformed in analogy to intermediate example 1a to give after working up and purification 264 mg (66%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): $\delta$= 0.51 (2H), 0.66 (2H), 2.34 (3H), 2.56-2.72 (2H), 2.81 (1H), 3.56 (2H), 3.68 (3H), 6.31 (1H), 6.86 (2H), 7.33 (1H), 7.38 (2H), 7.49 (1H), 7.93-8.02 (3H), 8.29 (1H) ppm.

Intermediate Example 9a

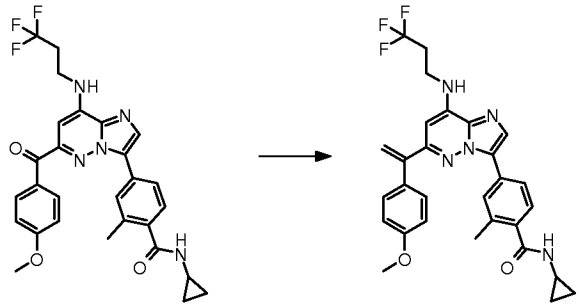
(*RS*)-*N*-Cyclopropyl-4-{6-[hydroxy(4-methoxyphenyl)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide



500 mg (1.16 mmol) *N*-cyclopropyl-4-{6-formyl-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 1c were transformed in analogy to intermediate example 1b using bromo(4-methoxyphenyl)magnesium to give after working up and purification 501 mg (72%) of the title compound.

**Example 10:**

***N*-Cyclopropyl-4-{6-[1-(4-methoxyphenyl)vinyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide**



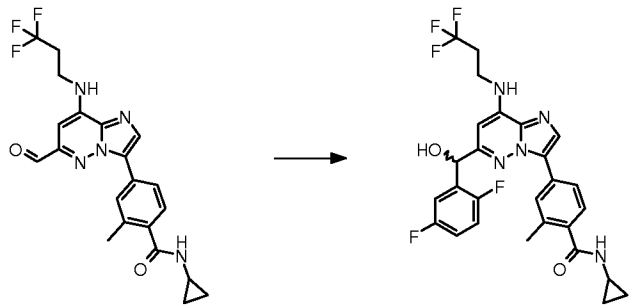
73 mg (136 µmol) *N*-cyclopropyl-4-{6-(4-methoxybenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to example 9 were transformed in analogy to example

1 to give after working up and purification 36.1 mg (45%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): δ= 0.47 (2H), 0.63 (2H), 2.17 (3H), 2.60-2.72 (2H), 2.78 (1H), 3.60 (2H), 3.76 (3H), 5.66 (1H), 5.85 (1H), 6.32 (1H), 6.93 (2H), 7.22 (1H), 7.35 (2H), 7.52 (1H), 7.84 (1H), 7.89 (1H), 8.00 (1H), 8.21 (1H) ppm.

**Example 11:**

**(*RS*)-*N*-Cyclopropyl-4-{6-[(2,5-difluorophenyl)(hydroxy)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide**

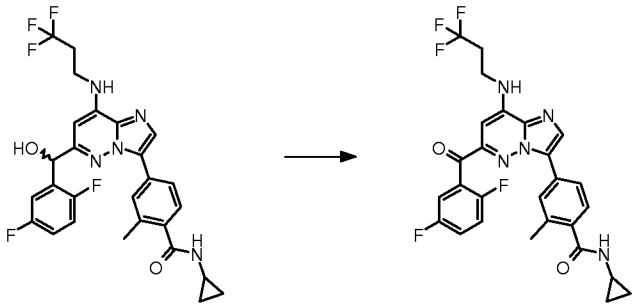


400 mg (927 µmol) *N*-cyclopropyl-4-{6-formyl-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 1c were transformed in analogy to intermediate example 1b using bromo(2,5-difluorophenyl)magnesium to give after working up and purification 326 mg (64%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): δ= 0.49 (2H), 0.65 (2H), 2.27 (3H), 2.58-2.74 (2H), 2.79 (1H), 3.60 (2H), 5.94 (1H), 6.41 (1H), 6.54 (1H), 7.12-7.27 (3H), 7.44 (1H), 7.57 (1H), 7.82 (1H), 7.88 (1H), 7.99 (1H), 8.26 (1H) ppm.

**Example 12:**

***N*-Cyclopropyl-4-{6-(2,5-difluorobenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide**

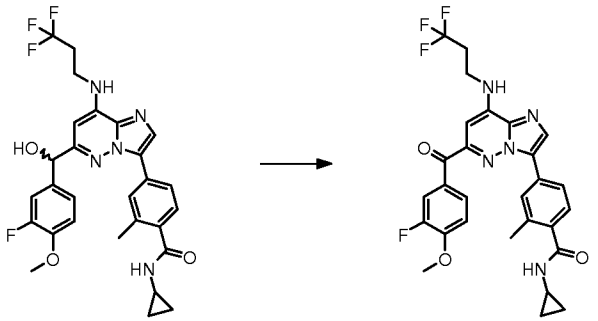


300 mg (550 µmol) (*RS*)-*N*-cyclopropyl-4-{6-[(2,5-difluorophenyl)(hydroxy)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to example 11 were transformed in analogy to intermediate example 1a to give after working up and purification 82 mg (27%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): δ= 0.48 (2H), 0.64 (2H), 2.14 (3H), 2.63-2.82 (3H), 3.71 (2H), 6.79 (1H), 7.18 (1H), 7.46 (1H), 7.55 (1H), 7.65 (1H), 7.73 (1H), 7.81 (1H), 7.99 (1H), 8.18 (1H), 8.23 (1H) ppm.

**Example 13:**

***N*-Cyclopropyl-4-{6-(3-fluoro-4-methoxybenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide**

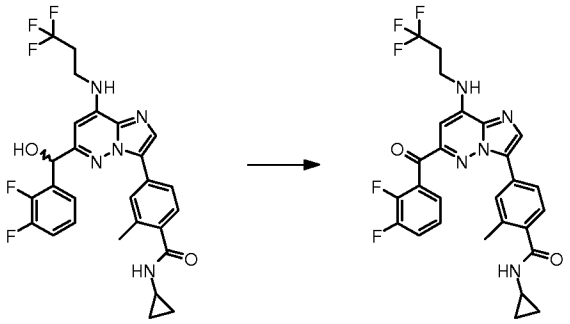


262 mg (470 µmol) *N*-cyclopropyl-4-{6-[(3-fluoro-4-methoxyphenyl)(hydroxy)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 1b were transformed in analogy to intermediate example 1a to give after working up and purification 210 mg (80%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): δ= 0.48 (2H), 0.64 (2H), 2.24 (3H), 2.64-2.75 (2H), 2.78 (1H), 3.68 (2H), 3.94 (3H), 6.67 (1H), 7.28 (1H), 7.34 (1H), 7.85 (1H), 7.89 (1H), 7.93-7.99 (3H), 8.13 (1H), 8.24 (1H) ppm.

**Example 14:**

***N*-Cyclopropyl-4-{6-(2,3-difluorobenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide**

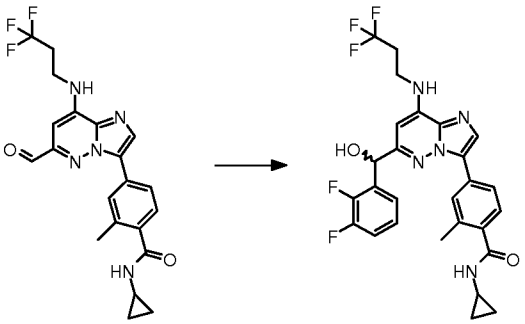


296 mg (543 µmol) *N*-cyclopropyl-4-{6-[(2,3-difluorophenyl)(hydroxy)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 14a were transformed in analogy to intermediate example 1a to give after working up and purification 165 mg (56%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): δ= 0.47 (2H), 0.64 (2H), 2.13 (3H), 2.63-2.82 (3H), 3.71 (2H), 6.80 (1H), 7.17 (1H), 7.40 (1H), 7.55 (1H), 7.68-7.84 (3H), 8.04 (1H), 8.19 (1H), 8.26 (1H) ppm.

Intermediate Example 14a

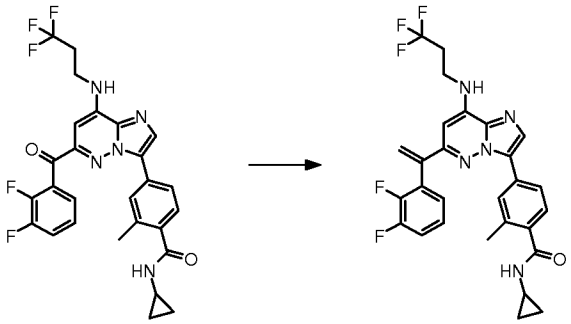
*N*-Cyclopropyl-4-{6-[(2,3-difluorophenyl)(hydroxy)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide



400 mg (927 µmol) *N*-cyclopropyl-4-{6-formyl-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 1c were transformed in analogy to intermediate example 1b using bromo(2,3-difluorophenyl)magnesium to give after working up and purification 326 mg (64%) of the title compound.

**Example 15:**

***N*-Cyclopropyl-4-{6-[1-(2,3-difluorophenyl)vinyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide**

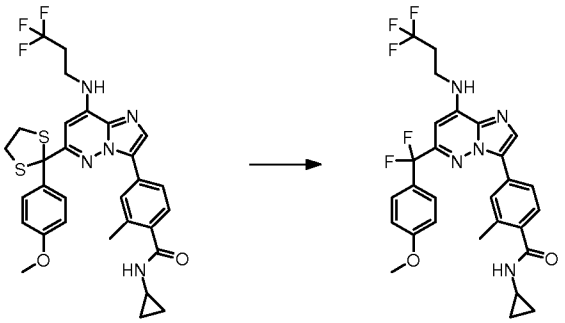


75 mg (138 µmol) *N*-Cyclopropyl-4-{6-(2,3-difluorobenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to example 14 were transformed in analogy to example 1 to give after working up and purification 67.2 mg (83%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): δ= 0.50 (2H), 0.66 (2H), 2.14 (3H), 2.68-2.83 (3H), 3.69 (2H), 5.81 (1H), 6.47 (1H), 6.65 (1H), 7.14 (1H), 7.22-7.32 (2H), 7.51 (1H), 7.58 (1H), 7.69 (1H), 7.75 (1H), 8.03 (1H), 8.24 (1H) ppm.

**Example 16:**

***N*-Cyclopropyl-4-{6-[difluoro(4-methoxyphenyl)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide**

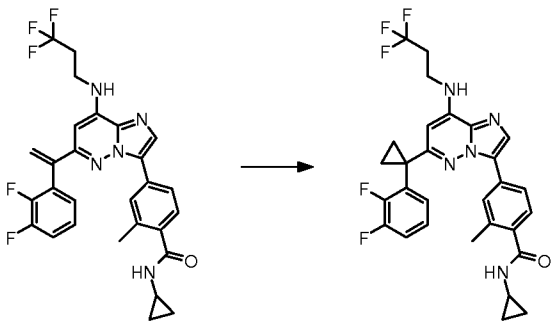


30 mg (49 µmol) *N*-cyclopropyl-4-{6-[2-(4-methoxyphenyl)-1,3-dithiolan-2-yl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 0.5a were transformed in analogy to example 2 to give after working up and purification 6.0 mg (21%) of the title compound.

$^1$H-NMR (DMSO-d$_6$): δ= 0.49 (2H), 0.65 (2H), 2.23 (3H), 2.61-2.84 (3H), 3.67 (2H), 3.77 (3H), 6.55 (1H), 7.04 (2H), 7.24 (1H), 7.55 (2H), 7.78 (2H), 7.94 (1H), 8.09 (1H), 8.26 (1H) ppm.

**Example 17:**

***N*-Cyclopropyl-4-{6-[1-(2,3-difluorophenyl)cyclopropyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide**



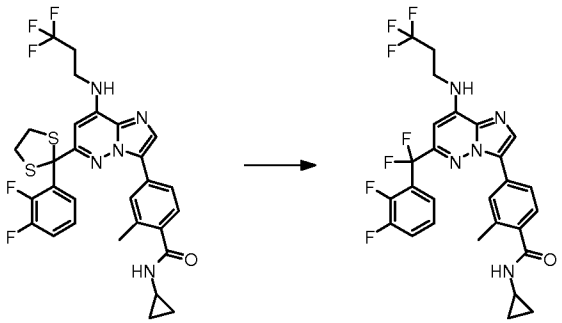
A mixture comprising 68.3 mg [iodo(dimethyl)oxido-lambda$^6$-sulfanyl]methane, 12.3 mg sodium hidride (60%) and 0.82 mL dimethyl sulfoxide was stirred at 60°C for 1.5 hours. A solution of 21 mg (39 µmol) *N*-cyclopropyl-4-{6-[1-(2,3-difluorophenyl)vinyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to example 15 in 0.43 mL dimethyl sulfoxide was added and stirring continued at 130°C under wicrowave irradiation for 1.5

hours. Water was added and the mixture extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. After filtration and removal of the solvent the residue was purified by chromatography to give 9.8 mg (41%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): $\delta$= 0.49 (2H), 0.65 (2H), 1.36 (2H), 1.65 (2H), 2.24 (3H), 2.50-2.67 (2H), 2.80 (1H), 3.52 (2H), 5.73 (1H), 7.16 (1H), 7.22 (1H), 7.30 (1H), 7.34-7.49 (2H), 7.74 (1H), 7.79 (1H), 7.96 (1H), 8.26 (1H) ppm.

**Example 18:**

**_N_-Cyclopropyl-4-{6-[(2,3-difluorophenyl)(difluoro)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide**

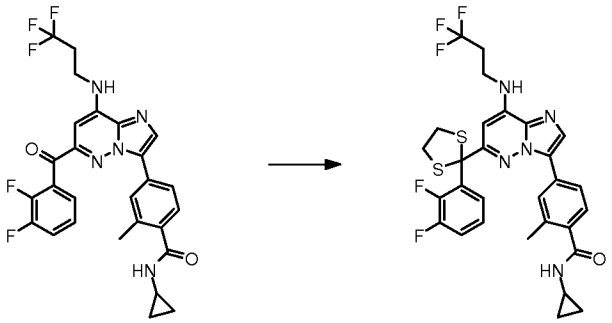


21 mg (34 µmol) _N_-cyclopropyl-4-{6-[2-(2,3-difluorophenyl)-1,3-dithiolan-2-yl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 18a were transformed in analogy to example 2 to give after working up and purification 7.8 mg (41%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): $\delta$= 0.48 (2H), 0.64 (2H), 2.15 (3H), 2.62-2.82 (3H), 3.71 (2H), 6.66 (1H), 7.14 (1H), 7.43 (1H), 7.56 (1H), 7.61 (1H), 7.65 (1H), 7.75 (1H), 8.07 (1H), 8.11 (1H), 8.26 (1H) ppm.

Intermediate Example 18a

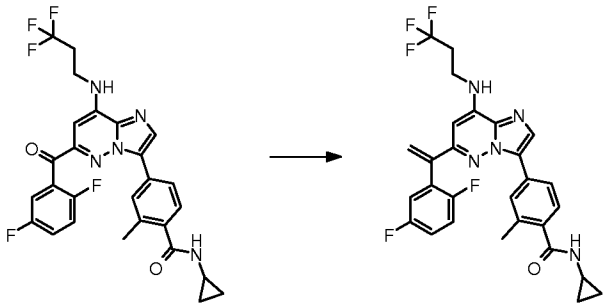
_N_-Cyclopropyl-4-{6-[2-(2,3-difluorophenyl)-1,3-dithiolan-2-yl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide



50 mg (92 µmol) *N*-cyclopropyl-4-{6-(2,3-difluorobenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to example 14 were transformed in analogy to intermediate example 0.2b to give after working up and purification 23.6 mg (41%) of the title compound.

**Example 19:**

**_N_-Cyclopropyl-4-{6-[1-(2,5-difluorophenyl)vinyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide**

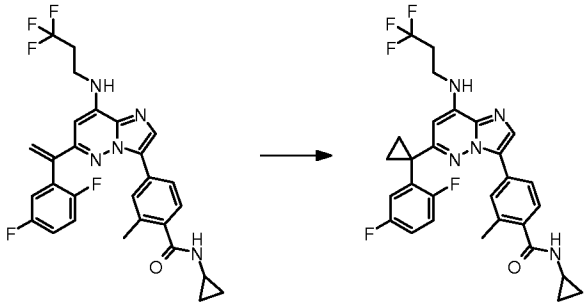


150 mg (276 µmol) *N*-cyclopropyl-4-{6-(2,5-difluorobenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to example 12 were transformed in analogy to example 1 to give after working up and purification 96.2 mg (61%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): $\delta$= 0.47 (2H), 0.64 (2H), 2.12 (3H), 2.62-2.81 (3H), 3.66 (2H), 5.78 (1H), 6.42 (1H), 6.61 (1H), 7.12 (1H), 7.23-7.35 (3H), 7.56 (1H), 7.67 (1H), 7.75 (1H), 8.01 (1H), 8.23 (1H) ppm.

**Example 20:**

**N-Cyclopropyl-4-{6-[1-(2,5-difluorophenyl)cyclopropyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide**

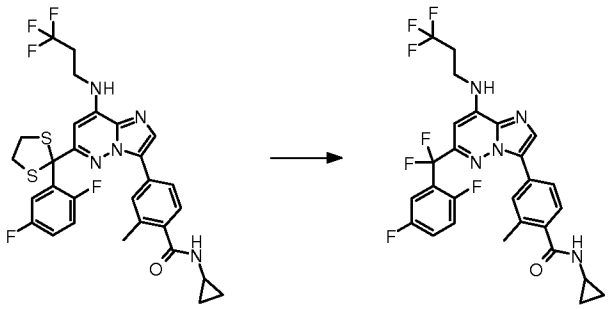


30 mg (55 µmol) *N*-cyclopropyl-4-{6-[1-(2,5-difluorophenyl)vinyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to example 19 were transformed in analogy to example 17 to give after working up and purification 9.9 mg (31%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): $\delta$= 0.50 (2H), 0.65 (2H), 1.36 (2H), 1.63 (2H), 2.26 (3H), 2.52-2.64 (2H), 2.80 (1H), 3.52 (2H), 5.75 (1H), 7.16-7.26 (3H), 7.35 (1H), 7.40 (1H) 7.75 (1H), 7.81 (1H), 7.95 (1H), 8.23 (1H) ppm.

**Example 21:**

**N-Cyclopropyl-4-{6-[(2,5-difluorophenyl)(difluoro)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide**

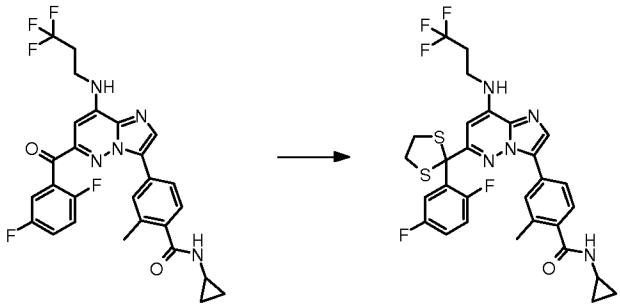


48 mg (77 µmol) *N*-cyclopropyl-4-{6-[2-(2,5-difluorophenyl)-1,3-dithiolan-2-yl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 21a were transformed in analogy to intermediate example 0.2b to give after working up and purification 17.3 mg (38%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): $\delta$= 0.48 (2H), 0.65 (2H), 2.16 (3H), 2.64-2.82 (3H), 3.71 (2H), 6.65 (1H), 7.16 (1H), 7.46 (1H), 7.56 (1H), 7.60-7.65 (2H), 7.67 (1H), 8.03 (1H), 8.11 (1H), 8.23 (1H) ppm.

Intermediate Example 21a

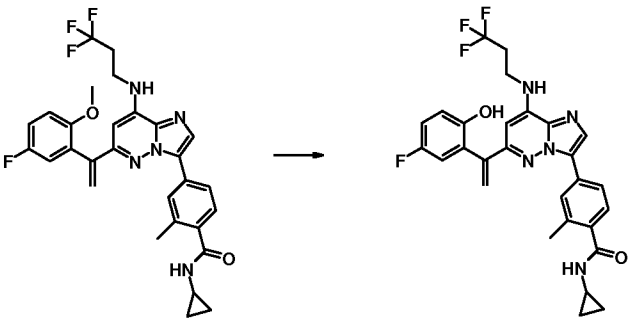
*N*-Cyclopropyl-4-{6-[2-(2,5-difluorophenyl)-1,3-dithiolan-2-yl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide



100 mg (184 µmol) *N*-cyclopropyl-4-{6-(2,5-difluorobenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to example 12 were transformed in analogy to intermediate example 0.2b to give after working up and purification 54 mg (47%) of the title compound.

**Example 22:**

**_N_-cyclopropyl-4-{6-[1-(5-fluoro-2-hydroxyphenyl)ethenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide**



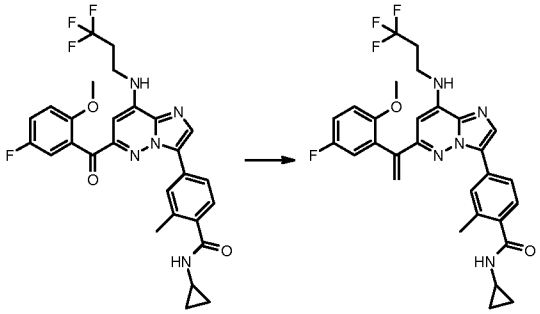
A mixture of 27.0 mg (49 µmol) *N*-cyclopropyl-4-{6-[1-(5-fluoro-2-methoxyphenyl)ethenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to

intermediate example 22a, 85.5 mg tribromoborane and 2000 µL DCM was stirred under ice cooling for 30 min and gave, after working-up and purification, 5.7 mg (22%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): δ= 0.44-0.52 (2H), 0.64 (2H), 2.15 (3H), 2.59-2.73 (2H), 2.78 (1H), 3.61 (2H), 5.59 (1H), 6.17 (1H), 6.41 (1H), 6.79 (1H), 7.00 (2H), 7.15 (1H), 7.41 (1H), 7.71-7.78 (1H), 7.84 (1H), 7.98 (1H), 8.20 (1H), 9.21 (1H) ppm.

Intermediate Example 22a

*N*-cyclopropyl-4-{6-[1-(5-fluoro-2-methoxyphenyl)ethenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide

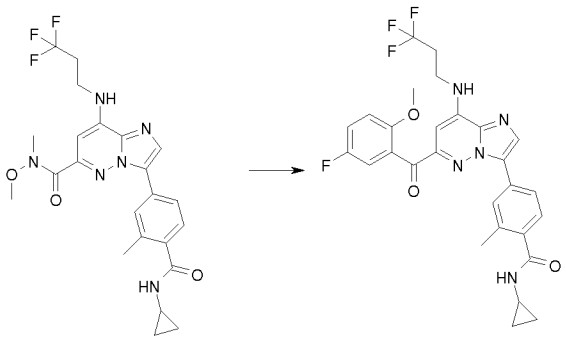


1740 mg (1.16 mmol) *N*-cyclopropyl-4-{6-(5-fluoro-2-methoxybenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 22b were transformed in analogy to example 1 to give after working up 1270 mg (73%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): δ= 0.43-0.52 (2H), 0.59-0.69 (2H), 2.14 (3H), 2.57-2.73 (2H), 2.73-2.84 (1H), 3.50 (3H), 3.56-3.67 (2H), 5.59 (1H), 6.25 (1H), 6.45 (1H), 6.98-7.16 (3H), 7.19 (1H), 7.46 (1H), 7.71 (1H), 7.78 (1H), 8.00 (1H), 8.23 (1H) ppm.

Intermediate Example 22b

*N*-cyclopropyl-4-{6-(5-fluoro-2-methoxybenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide

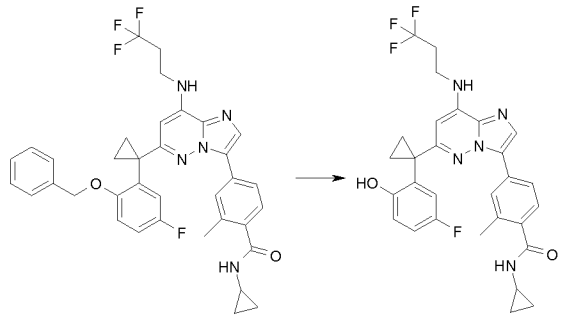


2000 mg (4.078 mmol) 3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-*N*-methoxy-*N*-methyl-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazine-6-carboxamide which was prepared according to intermediate example 0.3c were transformed in analogy to intermediate example 0.3b using bromo(5-fluoro-2-methoxyphenyl)magnesium to give after working up 1740 mg (77%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): δ= 0.43-0.51 (2H), 0.60-0.69 (2H), 2.13 (3H), 2.62-2.83 (4H), 3.60 (3H), 3.70 (2H), 6.75 (1H), 7.15 (1H), 7.21 (1H), 7.33-7.46 (2H), 7.72 (1H), 7.80 (1H), 7.92 (1H), 8.18 (1H), 8.25 (1H) ppm.

**Example 23:**

***N*-cyclopropyl-4-{6-[1-(5-fluoro-2-hydroxyphenyl)cyclopropyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide**



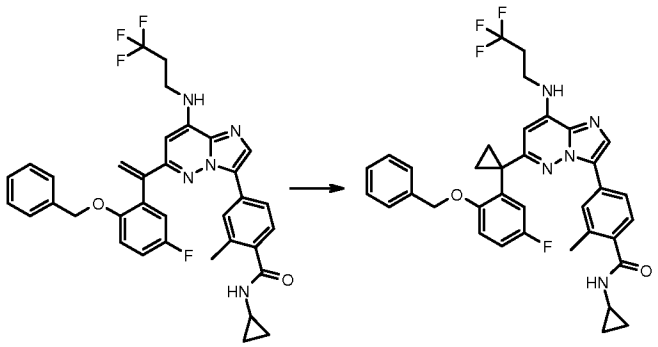
A mixture of 584 mg (907 µmol) 4-(6-{1-[2-(benzyloxy)-5-fluorophenyl]cyclopropyl}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl)-*N*-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 23a and 50 mg Pd/C in 50 mL

ethanol7HOAC 8:2 was stirred at rt under a hydrogen atmosphere at 1 atm for 8 days and gave, after working-up 68 mg (14%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): $\delta$= 0.47-0.58 (2H), 0.63-0.72 (2H), 1.21-1.29 (2H), 1.55-1.63 (2H), 2.51-2.65 (3H), 2.82 (1H), 3.46 (2H), 5.75 (1H), 6.81 (1H), 6.93-7.03 (1H), 7.11 (1H), 7.27 (1H), 7.37 (1H), 7.85-8.01 (3H), 8.30 (1H), 9.33 (1H) ppm.

Intermediate Example 23a

4-(6-{1-[2-(benzyloxy)-5-fluorophenyl]cyclopropyl}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl)-*N*-cyclopropyl-2-methylbenzamide

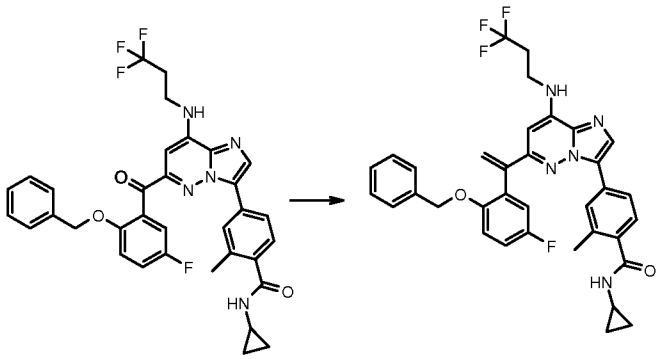


2060 mg crude (3.27 mmol) 4-(6-{1-[2-(benzyloxy)-5-fluorophenyl]ethenyl}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl)-*N*-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 23b were transformed in analogy to example 17 to give after working up and purification 692 mg (33%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): $\delta$= 0.49-0.57 (2H), 0.64-0.73 (2H), 1.26-1.33 (2H), 1.58-1.66 (2H), 2.31 (3H), 2.42-2.55 (2H), 2.83 (1H), 3.41 (2H), 4.98 (2H), 5.72 (1H), 6.97-7.04 (2H), 7.05-7.11 (4H), 7.14 (1H), 7.25-7.30 (2H), 7.32 (1H), 7.83-7.88 (1H), 7.92 (1H), 7.96 (1H), 8.26 (1H) ppm.

Intermediate Example 23b

4-(6-{1-[2-(benzyloxy)-5-fluorophenyl]but-3-en-1-yl}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl)-*N*-cyclopropyl-2-methylbenzamide

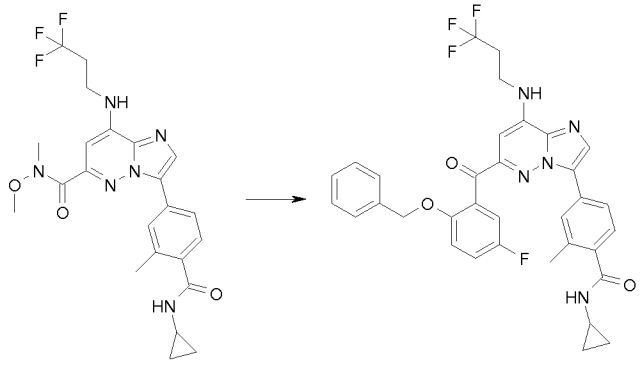


14.06 g (22.26 mmol) 4-{6-[2-(benzyloxy)-5-fluorobenzoyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-*N*-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 23c were transformed in analogy to example 1 to give after working up 21.83 g (150%) of the crude title compound which was used without further purification in the next step.

$^1$H-NMR (DMSO-$d_6$): $\delta$= 0.46-0.54 (2H), 0.62-0.70 (2H), 2.14 (3H), 2.52-2.68 (2H), 2.74-2.87 (1H), 3.59 (2H), 4.84 (2H), 5.65 (1H), 6.16 (1H), 6.39 (1H), 6.77 (2H), 6.93 (2H), 7.02-7.29 (5H), 7.43 (1H), 7.74 (1H), 7.82 (1H), 8.03 (1H), 8.21 (1H) ppm.

Intermediate Example 23c

4-{6-[2-(benzyloxy)-5-fluorobenzoyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-*N*-cyclopropyl-2-methylbenzamide

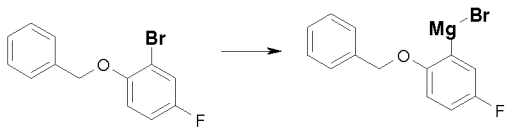


15.96 g (32.54 mmol) 3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-*N*-methoxy-*N*-methyl-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazine-6-carboxamide which was prepared according to intermediate example 0.3c in 300 mL THF were transformed in analogy to intermediate example 0.3b using a freshly prepared solution of [2-(benzyloxy)-5-fluorophenyl](bromo)magnesium (231 mmol in 200 mL THF) to give after working up 13.26 g (64.5%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): $\delta$= 0.47-0.56 (2H), 0.62-0.71 (2H), 2.12 (3H), 2.67 (2H), 2.80 (1H), 3.68 (2H), 4.96 (2H), 6.68 (1H), 6.83 (2H), 6.97 (2H), 7.07 (1H), 7.18 (1H), 7.32 (1H), 7.40-7.50 (2H), 7.73 (1H), 7.81 (1H), 7.88 (1H), 8.20 (1H), 8.24 (1H) ppm.

Intermediate Example 23d

[2-(benzyloxy)-5-fluorophenyl](bromo)magnesium

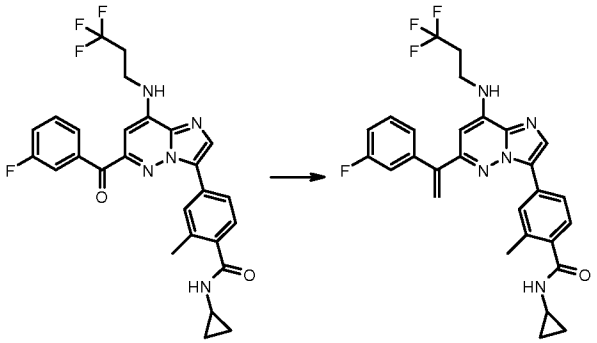


To stirred suspension of 5.62 g (231 mmol) magnesium in 100 mL THF were added at rt under an argon atmosphere one crystal of iodine and dropwise 40 mL of a solution of 64.95 g (231 mmol) 1-(benzyloxy)-2-bromo-4-fluorobenzene in 100 mL THF. The mixture was heated to 60°C until decolorization and the remaining solution of 1-(benzyloxy)-2-bromo-4-fluorobenzene was added dropwise while keeping the temperature at 50°C.

After cooling to rt, the Grignard solution was directly used for intermediate example 23c.

**Example 24:**

**_N_-cyclopropyl-4-{6-[1-(3-fluorophenyl)ethenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-_b_]pyridazin-3-yl}-2-methylbenzamide**

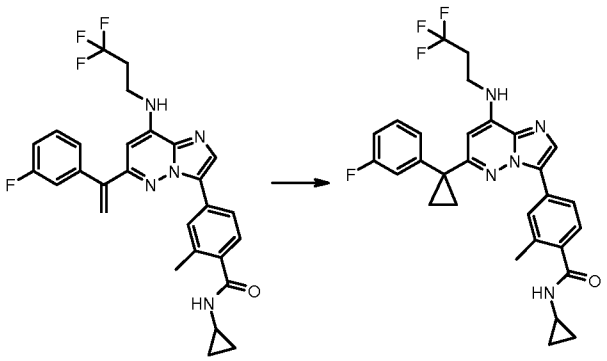


80.0 mg (152 µmol) _N_-cyclopropyl-4-{6-(3-fluorobenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-_b_]pyridazin-3-yl}-2-methylbenzamide which was prepared according to intermediate example 0.3b were transformed in analogy to example 1 to give after working up and purification 27 mg (33.7%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): δ= 0.44-0.51 (2H), 0.60-0.66 (2H), 2.16 (3H), 2.59-2.72 (2H), 2.77 (1H), 3.62 (2H), 5.81 (1H), 6.06 (1H), 6.41 (1H), 7.15-7.23 (2H), 7.23-7.30 (2H), 7.38-7.47 (1H), 7.55 (1H), 7.77-7.83 (1H), 7.85 (1H), 8.01 (1H), 8.20 (1H) ppm.

**Example 25:**

**_N_-cyclopropyl-4-{6-[1-(3-fluorophenyl)cyclopropyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-_b_]pyridazin-3-yl}-2-methylbenzamide**

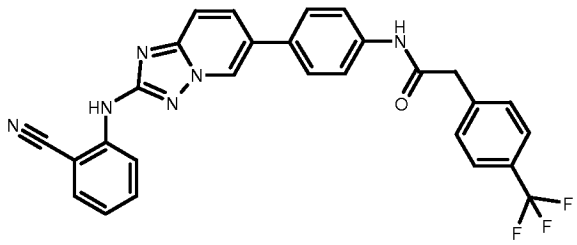


27.0 mg (52 µmol) *N*-cyclopropyl-4-{6-[1-(3-fluorophenyl)ethenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide which was prepared according to example 23 were transformed in analogy to example 1 to give after working up and purification 9 mg (32%) of the title compound.

$^1$H-NMR (DMSO-$d_6$): δ= 0.47-0.53 (2H), 0.61-0.69 (2H), 1.32-1.38 (2H), 1.54-1.59 (2H), 2.32 (3H), 2.57 (2H), 2.80 (1H), 3.51 (2H), 5.99 (1H), 7.03-7.11 (1H), 7.14-7.23 (2H), 7.27-7.40 (2H), 7.51 (1H), 7.84-7.91 (2H), 8.08 (1H), 8.26 (1H) ppm.

**Example 26:**

**N-(4-{2-[(2-cyanophenyl)amino][1,2,4]triazolo[1,5-a]pyridin-6-yl}phenyl)-2-[4-(trifluoromethyl)phenyl]acetamide**



To a stirred solution of **Int24.3** (60 mg) in DMF (3 mL) was added potassium carbonate (178 mg), [4-(trifluoromethyl)phenyl]acetic acid (57 mg) and TBTU (295 mg). The mixture was stirred at r.t. for 2 h. The mixture was concentrated in vacuum, water was added and the mixture was extracted with ethyl acetate and methanol (100 : 1). The organic phase was washed with

water and with saturated sodium chloride solution, dried (sodium sulfate) and the solvent was removed in vacuum. Recrystallization of the residue from ethanol gave 27 mg of the title compound.

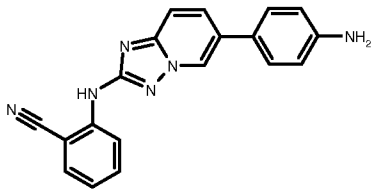
$^1$H-NMR (300MHz, DMSO-$d_6$): δ [ppm]= 3.77 (s, 2H), 7.14 (td, 1H), 7.54 (d, 2H), 7.58 - 7.76 (m, 9H), 7.89 (dd, 1H), 7.99 (d, 1H), 9.06 (br. s, 1H), 9.47 (s, 1H), 10.33 (br. s, 1H).

Analytical UPLC-MS was performed as follows:

Method A: System: UPLC Acquity (Waters) with PDA Detector und Waters ZQ mass spectrometer; Column: Acquity BEH C18 1.7µm 2.1x50mm; Temperature: 60°C; Solvent A: Water + 0.1% formic acid; Solvent B: acetonitrile; Gradient: 99 % A → 1 % A (1.6 min) → 1 % A (0.4 min) ; Flow: 0.8 mL/min; Injection Volume: 1.0 µl (0.1mg-1mg/mL sample concentration); Detection: PDA scan range 210-400 nm - Fixed and ESI (+), scan range 170-800 m/z

Intermediate Example Int24.3

2-{[6-(4-aminophenyl)[1,2,4]triazolo[1,5-a]pyridin-2-yl]amino}benzonitrile

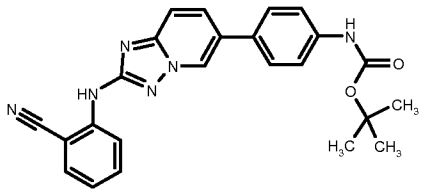



To a stirred suspension of **Int24.2** (2.0 g) in DCM (100 mL) and acetic acid (46 mL) was added 1,3-dimethoxybenzene (6.0 mL) and borontrifluoride diethyletherate (2.4 mL). The mixture was stirred at r.t. for 2 h. The mixture was poured into a half-saturated solution of potassium carbonate (400 mL) and was extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried (sodium sulfate) and the solvent was removed in vacuum. Silica gel chromatography gave 943 mg of the title compound.

$^1$H-NMR (400MHz, DMSO-$d_6$): δ [ppm]= 5.29 (s, 2H), 6.62 (d, 2H), 7.09 - 7.16 (m, 1H), 7.42 (d, 2H), 7.56 (d, 1H), 7.59 - 7.67 (m, 1H), 7.71 (dd, 1H), 7.80 (dd, 1H), 8.00 (d, 1H), 8.88 (d, 1H), 9.39 (s, 1H).

Intermediate Example Int24.2.

tert-butyl (4-{2-[(2-cyanophenyl)amino][1,2,4]triazolo[1,5-a]pyridin-6-yl}phenyl)carbamate

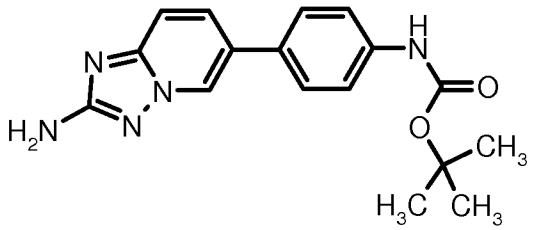


To a stirred solution of **Int01.03** (8.0 g) in toluene (95 ml) was added 2-bromobenzonitril (6.33 g), $Pd_2dba_3$ (1.13 g) and rac-BINAP (1.56 g). The flask was twice degased and backfilled with argon. The mixture was stirred at r.t. for 5 minutes. Caesium carbonate (24.3 g) was added, the flask was twice degased and backfilled with argon and the mixture was heated to reflux for 3h. Water was added and the reaction mixture was extracted with ethyl acetate and methanol (10:1). The organic phase was washed with water, dried (sodium sulfate) and the solvent was removed in vacuum. Silica gel chromatography gave a white solid, that was recrystallized from ethanol.
Yield: 5.8 g of the title compound.

$^1$H-NMR (400MHz, DMSO-$d_6$): δ [ppm]= 1.46 (s, 9H), 7.11 (t, 1H), 7.53 (d, 2H), 7.57 - 7.68 (m, 4H), 7.70 (d, 1H), 7.87 (dd, 1H), 8.00 (d, 1H), 9.03 (s, 1H), 9.47 (br. s., 2H).

Intermediate Example Int01.03.

*tert*-butyl [4-(2-amino[1,2,4]triazolo[1,5-*a*]pyridin-6-yl)phenyl]carbamate

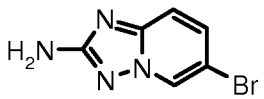


To a stirred solution of **Int01.02** (5.82 g) in 1-propanol (400 mL) was added 2M potassium carbonate solution (41 mL), {4-[(*tert*-butoxycarbonyl) amino] phenyl} boronic acid (8.6 g), triphenylphosphine (150 mg) and $PdCl_2(PPh_3)_2$ (1.9 g). The mixture was heated to reflux for 4 h, the solvent was removed in vacuum, water (150 mL) was added and the mixture was extracted with ethyl acetate (500 mL). The organic phase was dried (sodium sulfate), filtered through Celite and the solvent was removed in vacuum. The residue was triturated with DCM to give the title compound as a white solid. Yield: 7.2 g.

$^1$H-NMR (400MHz, DMSO-$d_6$): δ [ppm]= 1.37 - 1.55 (m, 9H), 5.99 (s, 2H), 7.36 (dd, 1H), 7.48 - 7.55 (m, 2H), 7.55 - 7.62 (m, 2H), 7.69 (dd, 1H), 8.78 (dd, 1H), 9.44 (s, 1H).

Intermediate Example Int01.02

6-Bromo[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



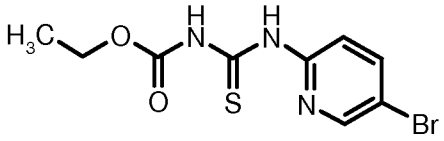
Hydroxylammoniumchlorid (39.8 g) was suspended in methanol (200 mL) and ethanol (190 mL) and Hünig Base (59 mL) was added at r.t. The mixture was heated to 60°C, **Int01.01** (30 g) was added portionwise, and the mixture was stirred at 60°C for 2h. The solvent was removed in vacuum and water (150 mL) was added. A solid was collected by filtration and was washed with water and dried in vacuum.

Yield: 19.3 g of the title compound.

$^1$H-NMR (300MHz, DMSO-$d_6$): δ [ppm]= 6.10 (s, 2H), 7.28 (dd, 1H), 7.51 (dd, 1H), 8.88 (dd, 1H).

Intermediate Example Int01.01

Ethyl [(5-bromopyridin-2-yl)carbamothioyl]carbamate



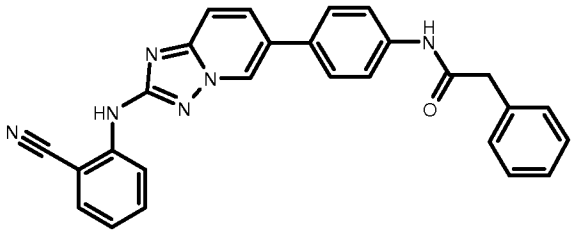
Ethoxycarbonylisothiocyanat (16.7 g) was added to a stirred solution of 2-amino-5-brompyridine (20 g) in dioxane (200 mL). The mixture was stirred for 2h at r.t. A white solid precipitated. Hexane (20 mL) was added and the white solid was collected by filtration.

Yield: 30.4 g of the title compound.

$^1$H-NMR (300MHz, DMSO-$d_6$): δ [ppm]= 1.22 (t, 3H), 4.19 (q, 2H), 8.08 (dd, 1H), 8.49 (d, 1H), 8.57 (br. d, 1H), 11.37 - 12.35 (m, 2H).

**Example 27 (BAY 2):**

**N-(4-{2-[(2-cyanophenyl)amino][1,2,4]triazolo[1,5-a]pyridin-6-yl}phenyl)-2-phenylacetamide**



Starting with **Int24.3**, **Example 27** was prepared analogously to the procedure for the preparation of **Example 26**.

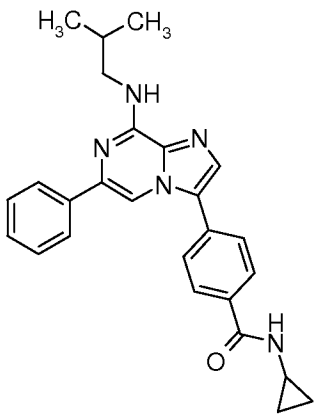
$^1$H-NMR: (300MHz, DMSO-$d_6$): δ [ppm]= 3.64 (s, 2H), 7.14 (td, 1H), 7.18 - 7.36 (m, 5H), 7.58 - 7.75 (m, 7H), 7.89 (dd, 1H), 7.99 (d, 1H), 9.06 (d, 1H), 9.49 (s, 1H), 10.28 (s, 1H).

Analytical UPLC-MS was performed as follows:

Method A: System: UPLC Acquity (Waters) with PDA Detector und Waters ZQ mass spectrometer; Column: Acquity BEH C18 1.7µm 2.1x50mm; Temperature: 60°C; Solvent A: Water + 0.1% formic acid; Solvent B: acetonitrile; Gradient: 99 % A → 1 % A (1.6 min) → 1 % A (0.4 min) ; Flow: 0.8 mL/min; Injection Volume: 1.0 µl (0.1mg-1mg/mL sample concentration); Detection: PDA scan range 210-400 nm - Fixed and ESI (+), scan range 170-800 m/z

**Example 28:**

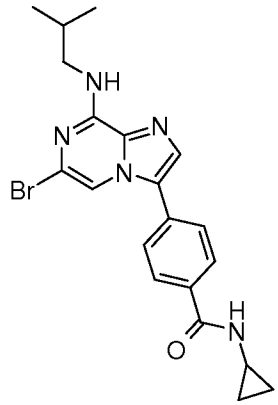
**Preparation of N-cyclopropyl-4-(8-isobutylamino-6-phenyl-imidazo [1,2-a]pyrazin-3-yl)-benzamide**



0.1 mmol intermediate example Int26.1 (1 mL, 0.1 M in NMP), 0.15 mmol phenylboronic acid (0.3 mL, 0.5 M in NMP, 1.5 eq), 0.01 mmol $Pd(OAc)_2$ (0.267 mL, 0.0375M in NMP, 0.1 eq), 0.02 mmol $P(oTol)_3$ (0.4 mL, 0.05M in NMP, 0.2 eq) and 0.3 mmol $K_2CO_3$ (0.3 mL, 1M in water, 3 eq) were combined in a sealed vial and heated at 140 °C under microwave irradiation for 80 min. After cooling, the solution was filtered and subjected to preparative HPLC to give 11.8 mg (25 %) N-cyclopropyl-4-(8-isobutylamino-6-phenyl-imidazo[1,2-a] pyrazin-3-yl)-benzamide: $^1$H-NMR (300 MHz, $d_6$-DMSO): $\delta$ = 8.52 (1H, d), 8.10 (1H, s), 7.99 - 7.93 (4H, m), 7.82 - 7.75 (3H, m), 7.72 (1H, tr), 7.44 - 7.28 (3H, m), 3.40 (2H, tr), 2.85 (1H, m), 2.10 (1H, m), 1.07 - 0.90 (7H, m), 0.68 (2H, m), 0.56 (2H, m) ppm; UPLC-MS: RT = 1.42 min; m/z (ES+) 426.5 [$MH^+$]; required MW = 425.5.

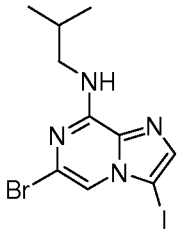
Intermediate Example Int26.1

Preparation of 4-(6-bromo-8-isobutylamino-imidazo[1,2-a]pyrazin-3-yl)-N-cyclopropyl-benzamide



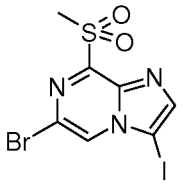
To a stirred solution of (6-bromo-3-iodo-imidazo[1,2-a]pyrazin-8-yl)-isobutyl-amine (74.20 g, 188 mmol) in dioxane (1300 mL) was subsequently added 130 mL water, 119 g tripotassium phosphate (563 mmol, 3 eq), 50.06 g [4-[(cyclopropylamino)carbonyl]phenyl]-boronic acid (244 mmol, 1.3 eq) and 7.42 g $Pd(dppf)Cl_2$ (9 mmol, 0.05 eq) in one portion at rt under argon atmosphere. After stirring for 72 h at 40° C, the mixture was poured on 5 L water and the precipitate was filtered off and washed with water. The precipitate was taken up in DCM, washed with sat. sodium chloride solution, dried over sodium sulphate and after filtration the solvent was evaporated. Purification by flash chromatography (DCM / acetone 95:5) yielded 45.2 g (56.20 %) 4-(6-bromo-8-isobutylamino-imidazo[1,2-a]pyrazin-3-yl)-N-cyclopropyl-benzamide: $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ = 7.90 (2H, d), 7.65 (1H, s), 7.58 (2H, d), 7.56 (1H, s), 6.32 (1H, s), 6.20 (1H, tr), 3.46 (2H, dd), 2.95 (1H, m), 2.01 (1H, m), 1.04 (6H, d), 0.92 (2H, m), 0.66 (2H, m) ppm.

**Preparation of (6-bromo-3-iodo-imidazo[1,2-a]pyrazin-8-yl)-isobutyl-amine**



To a stirred solution of 6-bromo-3-iodo-8-methanesulfonyl-imidazo[1,2-a] pyrazine (5.08 g, 12.64 mmol) in NMP (100 mL) was added 3.77 mL isobutylamine (2.77 g, 37.90 mmol, 3 eq) in one portion at rt. After stirring for 2 h at rt, 500 mL water was added and the mixture was extracted with ethyl acetate (3 x 200 mL). The organic phase was filtered, evaporated and the residue was recrystallized from MeOH / water to yield 3.87 g (77.52 %) (6-bromo-3-iodo-imidazo[1,2-a]pyrazin-8-yl)-isobutyl-amine: $^1$H-NMR (300 MHz, $d_6$-DMSO): $\delta$ = 8.09 (1H, tr), 7.60 (1H, s), 7.54 (1H, s), 3.19 (2H, dd), 1.95 (1H, m), 0.85 (6H, d) ppm.

**Preparation of 6-bromo-3-iodo-8-methanesulfonyl-imidazo[1,2-a]pyrazine**



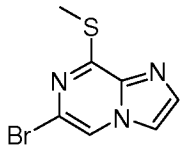
To a stirred solution of 6-bromo-3-iodo-8-methylsulfanyl-imidazo[1,2-a] pyrazine (100.0 g, 270.3 mmol) in DCM (2000 mL) was added meta-chloro perbenzoic acid (116.6 g, 675.6 mmol, 2.5 eq) in several portions at 0 °C. After stirring for 1 h at rt, another equivalent of meta-chloro perbenzoic acid (46.64 g, 270.3 mmol) was added and the mixture was stirred overnight. The suspension was filtered and the organic phase was washed with water (2L), saturated NaHCO3 solution (2L), sole (2L), dried over sodium sulphate, filtered and evaporated to yield 197 g of an orange solid. The solid was refluxed in ethanole (300 mL) for 15 min, filtered and dried at 50° C in vaccuo to yield 104.5 g (96.2 %) 6-bromo-3-iodo-8-methanesulfonyl-imidazo[1,2-a]pyrazine as

a yellowish solid: $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ = 8.45 (1H, s), 8.07 (1H, s), 3.54 (3H, s) ppm.

**Preparation of 6-bromo-3-iodo-8-methylsulfanyl-imidazo[1,2-a]pyrazine**

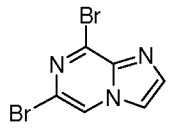
To a stirred solution of 6-bromo-8-methylsulfanyl-imidazo[1,2-a]pyrazine (210.0 g, 860.3 mmol) in DMF (4200 mL) was added NIS (212.9 g, 946.3 mmol, 1.1 eq) in one portion at rt. After 18 h stirring at 60°C the dark solution was evaporated and the brown residue was dissolved in DCM (7 L), washed with water (2 x 5L) and sole (2 x 5L) and dried over sodium sulphate. Crystallization by careful removal of solvent yielded 255 g (80.1 %) 6-bromo-3-iodo-8-methylsulfanyl-imidazo[1,2-a]pyrazine: $^1$H-NMR (300 MHz, $d_6$-DMSO): $\delta$ = 8.24 (1H, s), 7.79 (1H, s), 2.46 (3H, s) ppm.

**Preparation of 6-bromo-8-methylsulfanyl-imidazo[1,2-a]pyrazine**



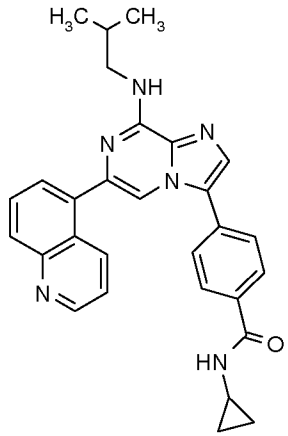
To a stirred suspension of intermediate example 1-1 6,8-dibromo-imidazo[1,2-a]pyrazine (489 g, 1766 mmol) in MeOH (2900 mL) at -20°C was dropwise added a solution of sodium methan thiolate (225 g, 3214 mmol, 1.8 eq) in 800 mL water. After stirring overnight, the clear solution was poured on 30 L water and the yellowish precipitate was filtered, washed with 3 L water and dried in vaccuo to yield 301 g 6-bromo-8-methylsulfanyl-imidazo[1,2-a]pyrazine (69.8 %). $^1$H-NMR (300 MHz, $d_6$-DMSO): $\delta$ = 8.64 (1H, s), 8.00 (1H, d), 7.66 (1H, d2.54 (3H, s) ppm.

**Preparation of 6,8-dibromo-imidazo[1,2-a]pyrazine**



To a stirred suspension of 2-amino-3,5-dibrompyrazine (427 g, 1688mmol) in water (6.4 L) / THF (482 mL), at rt was added bromacetaldehyde-diethylacetal (998 g, 5065 mmol) in one portion. After stirring under reflux for 4 h, the clear orange solution was stirred for an additional 15 h at rt. The suspension was filtered, and the remaining solid was washed with MeOH (2 L) and dried in vaccuo at 60°C to yield 6,8-dibromo-imidazo[1,2-a]pyrazine as an off-white solid (500 g, 107% with residual MeOH): $^1$H-NMR (300 MHz, $d_6$-DMSO): $\delta$ =9.02 (s, 1H), 8.23 (d, 1H), 7.89 (d, 1H) ppm. UPLC-MS: RT = 0.80 min; m/z 277.9 [$MH^+$]; required MW = 276.9.

**Example 29 (BAY 3):**
**N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(quinolin-5-yl)imidazo[1,2-a] pyrazin-3-yl}benzamide**



**Example 29** (BAY 3) was prepared analogously to the procedure described for **Example 28** using the intermediate example Int26.1 and the appropriate boronic acid building block.

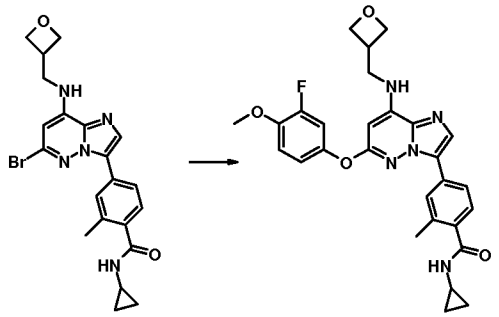
Analytical UPLC-MS was performed as follows:

Method A: System: UPLC Acquity (Waters) with PDA Detector and Waters ZQ mass spectrometer; Column: Acquity BEH C18 1.7µm 2.1x50mm; Temperature: 60°C; Solvent A: Water + 0.1% formic acid; Solvent B: acetonitrile; Gradient: 99 % A → 1 % A (1.6 min) → 1 % A (0.4 min) ; Flow: 0.8 mL/min; Injection Volume: 1.0 µl (0.1mg-1mg/mL sample concentration); Detection: PDA scan range 210-400 nm - Fixed and ESI (+),scan range 170-800 m/z

RT = 1.10 MWfound = 477.6 MWcalc = 476.6

**Example 30:**

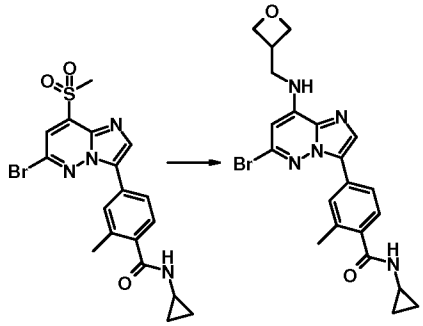
**N-cyclopropyl-4-{6-(3-fluoro-4-methoxyphenoxy)-8-[(oxetan-3-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide**



A solution of 128 mg (900 µmol) of 3-fluoro-4-methoxyphenol in 2 mL of dimethylsulfoxide was treated with 36 mg (900 µmol) of sodium hydride and stirred at room temperature for 1 hour. Then 68 mg (150 µmol) of 4-{6-bromo-8-[(oxetan-3-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide, which was prepared according to intermediate example 30a, was added and the mixture was heated for 1 h at 130°C and overnight at 120°C to give after HPLC purification 17 mg (20%) of the title compound.
$^1$H-NMR (DMSO-d6): δ= 0.43-0.50 (2H), 0.59-0.68 (2H), 2.11 (3H), 2.77 (1H), 3.35 (1H), 3.61 (2H), 3.83 (3H), 4.34 (2H), 4.63 (2H), 6.09 (1H), 7.02-7.09 (1H), 7.13-7.25 (2H), 7.30 (1H), 7.61-7.68 (1H), 7.77 (1H), 7.83 (1H), 7.91 (1H), 8.22 (1H)ppm.

Intermediate Example 30a

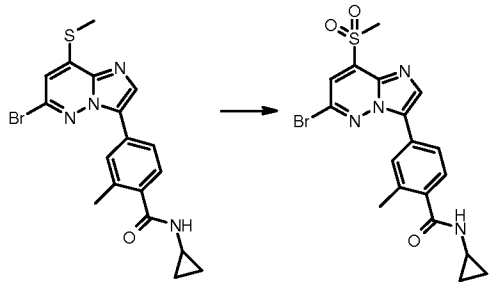
4-{6-bromo-8-[(oxetan-3-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide



To a suspension of 3000 mg (6677 µmol) 4-[6-bromo-8-(methylsulfonyl)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide, which was prepared according to intermediate example 30b in 150 mL of THF were added 873 mg (1002 µmol) 1-(oxetan-3-yl)methanamine and 2589 mg (2003 µmol) DIPEA and the mixture was heated for 72 hours at 60°C. After further addition of 100 mg 1-(oxetan-3-yl)methanamine and heating for 8 h at 60°C, the solvent was removed in vaccuo and the residue was taken up in ethyl acetate and washed with water. The precipitate formed was filtered off to yield 0.99 g (33%) of the title compound. The remaining aqueous phase was reextracted with DCM, and the combined organic phases were evaporated. The residue was triturated with THF at 75°C to yield another 1.65 g (53%) of the title compound.
$^1$H-NMR (DMSO-d6): δ= 0.46-0.53 (2H), 0.61-0.69 (2H), 2.35 (3H), 2.75-2.85 (1H), 3.25 (1H), 3.54-3.69 (2H), 4.31 (2H), 4.62 (2H), 6.45 (1H), 7.36 (1H), 7.84 (1H), 7.90 (1H), 7.94 (1H), 8.12 (1H), 8.30 (1H) ppm.

Intermediate Example 30b

4-[6-bromo-8-(methylsulfonyl)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide

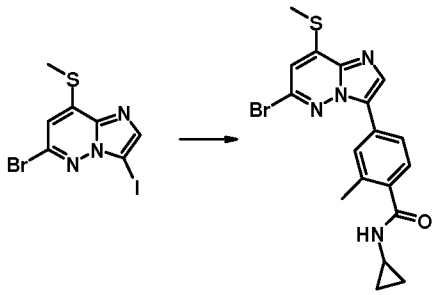


To a solution of 12.5 g (28.75 mmol) 4-[6-bromo-8-(methylsulfanyl)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide, which was prepared according to intermediate example 30c in 400 mL of DMF were added 53.03 g (86.26 mmol) potassium hydrogen sulfate sulfate (hydroperoxysulfonyl)oxidanide (5:1:1:2) and the mixture was stirred overnight at rt. to give, after aqueous work-up, 8.6 g (60%) of the title compound (impurity is 4-[6-bromo-8-(methylsulfinyl)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide)

UPLC-MS: RT = 0.98 min; m/z (ES+) 450.3 [MH+]; required MW = 449.3.

Intermediate Example 30c

4-[6-bromo-8-(methylsulfanyl)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide



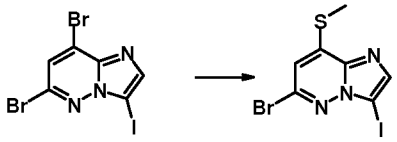
A mixture comprising 55.69 g (150 mmol) 6-bromo-3-iodo-8-(methylsulfanyl)imidazo[1,2-b]pyridazine which was prepared according to intermediate example 30d, 68 g (225 mmol) N-cyclopropyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide, which was prepared according to intermediate example 30g, 11 g (15 mmol) (1,1,-bis(diphenylphosphino)ferrocene)-dichloropalladium (II), 450 mL aqueous 1M potassium carbonate solution and 632 mL tetrahydrofuran was stirred at 60°C

for 12 hours to give, after aqueous workup, 130 g crude product. The residue was triturated with DCM to yield 15.15 g (24%) of the title compound. The filtrate was purified by chromatography to give another 2.65g (3%) of the title compound.

$^1$H-NMR (DMSO-d6): δ= 0.47-0.54 (2H), 0.62-0.71 (2H), 2.36 (3H), 2.63 (3H), 2.77-2.85 (1H), 7.17 (1H), 7.40 (1H), 7.85 (1H), 7.90 (1H), 8.12 (1H), 8.31 (1H) ppm.

Intermediate Example 30d

6-bromo-3-iodo-8-(methylsulfanyl)imidazo[1,2-b]pyridazine

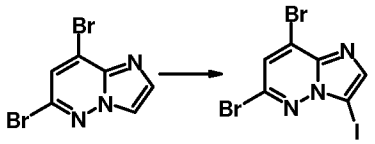


To a solution of 174 g (432 mmol) 6,8-dibromo-3-iodoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 30e in 3.8 L dioxane were added 30.28 g (432 mmol) sodium methanethiolate and the mixture was stirred at 60°C for 5 days. Further 25 g sodium methanethiolate were added and the mixture was stirred at 80°C for 2h. After cooling, the solution was poured on 4 L water Water and the aqueous phase was extracted with ethyl acetate. The organic phase was washed with water, dried over sodium sulphate, filtered and evaporated to give 102 g (64%) of the title compound.

$^1$H-NMR (DMSO-d6): δ= 6.79 (1H), 7.67 (1H)ppm.

Intermediate Example 30e

6,8-dibromo-3-iodoimidazo[1,2-b]pyridazine



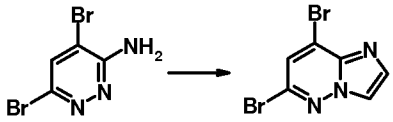
To a mixture comprising 156 g (563 mmol) 6,8-dibromoimidazo[1,2-b]pyridazine which was prepared according to intermediate example 30f, 190 g (1637 mmol) N-iodosuccinimide and 1.3 L chloroform were added 5.5 mL HCl

conc and the suspension was heated at 70°C overnight. The precipitate was filtered off and triturated with diisopropylether to give 119 g (52%) of the title compound.

$^1$H-NMR (DMSO-d6): δ= 7.92 (1H), 8.00 (1H) ppm.

Intermediate Example 30f

6,8-dibromoimidazo[1,2-b]pyridazine

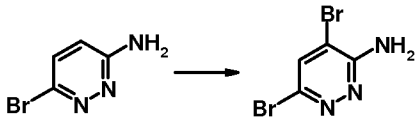


A mixture comprising 235 g (931 mmol) 4,6-dibromopyridazin-3-amine which was prepared according to intermediate example 30g, 421 mL (2792 mmol) 2-bromo-1,1-diethoxyethane, 2.93 L water and 227 mL THF was heated at 125°C for for h and at rt overnight.The solution was neutralized by addition of solid $NaHCO_3$, the precipitate was filtered off, washed with water and dried to give 156 g (80%) of the title compound as a brownish solid.

$^1$H-NMR (DMSO-d6): δ= 7.81 (1H), 8.40 (1H) ppm.

Intermediate Example 30g

6,8-dibromoimidazo[1,2-b]pyridazine

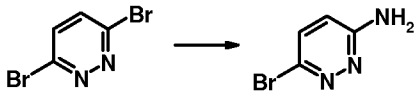


To a mixture comprising 285 g (1638 mmol) 6-bromopyridazin-3-amine which was prepared according to intermediate example 30h,275 g (3276 mmol) $NaHCO_3$ and 2815 mL MeOH was dropwise added 85 mL (1638 mmol) bromine at rt and it was stirred at rt overnight. After further addition of 34 mL (655 mmol) bromine and 55 g (655 mmol) $NaHCO_3$,the mixture was stirred overnight again. The solvent was reduced to about 1000 mL and the mixture was poured on 5 L of water. The precipitate was filtered off, washed with water and dried give 411 g (99%) of the title compound.

$^1$H-NMR ($CDCl_3$): δ= 6.14 (1H), 9.92 (2H) ppm.

Intermediate Example 30h

6-bromopyridazin-3-amine

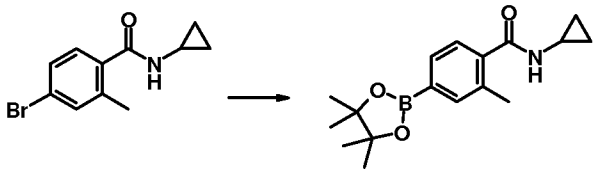


A solution of 250 g (1.05 mol) 3,6-dibromopyridazine in 1.2 L 25% aqueous ammonia was heated to 100°C at 11.7 bar overnight in an autoclave. After cooling, the precipitate was filtered off, washed with water and dried to give 137 g (75%) of the title compound.

$^1$H-NMR (DMSO-d6): δ= 6.58 (1H), 6.69 (2H), 7.41 (1H) ppm.

Intermediate Example 30i

N-cyclopropyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide



To a solution of 260g (1.02 mol) 4-bromo-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 30j in 2L dioxane at 23°C were added 390g bis-(pinacolato)-diboron, 19.5g 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, 150.g potassium acetate and 9.37 g tris-(dibenzylidenaceton)-dipalladium(0) and the mixture was refluxed for 6 h. After cooling to 23°C, water and ethyl acetate were added and the mixture stirred for 15 min. The organic phase was washed with water, dried over sodium sulfate, filtered and evaporated. The residue was purified by chromatography to give 308g (56%) of the title compound.

$^1$H-NMR (300 MHz, $CDCl_3$): δ = 0.59 (2H), 0.85 (2H), 1.33 (6H), 2.41 (3H), 2.87 (1H), 5.94 (1H), 7.28 (1H), 7.60 (1H), 7.63 (1H) ppm.

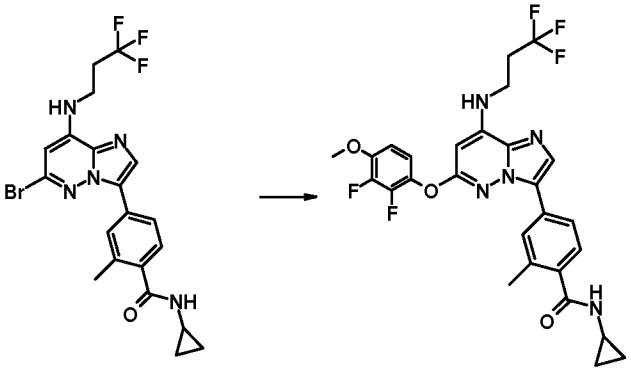
Intermediate Example 30j

4-Bromo-N-cyclopropyl-2-methylbenzamide

To a stirred solution of 300g (1.4 mol) 4-bromo-2-methylbenzoic acid in 8.4L dichloromethane at 23°C were added 79.6g cyclopropanamine and 320.9g EDC. After stirring overnight, the solution was washed with water and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over sodium sulfate, filtered and evaporated. The remaining solid was triturated with diisopropyl ether, filtered, washed and dried in vaccuo to yield 260g (73%)of the title compound.

**Example 31:**

**N-cyclopropyl-4-{6-(2,3-difluoro-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide**

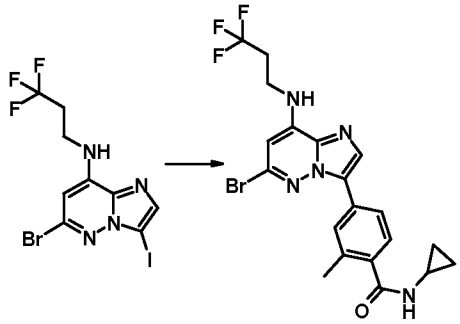


A solution of 31.9 g (199 mmol) 2,3-difluoro-4-methoxyphenol in 450 mL of dimethylsulfoxide was treated with 7.96 g (199 mmol) of sodium hydride and stirred at room temperature for 1 hour. Then 16 g (33.2 mmol) of 4-{6-bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide, which was prepared according to intermediate example 31a, was added and the mixture was heated overnight at 130°C. After cooling, 300 mL ethyl acetate were added and the organic phase is washed with water. After evaporation of the organic phase, the residue was triturated with 200 mL EtOH to give 12.05 g (65%) of the title compound.

$^1$H-NMR (DMSO-d6): δ= 0.47-0.53 (2H), 0.62-0.70 (2H), 2.11 (3H), 2.72 (2H), 2.80 (1H), 3.64 (2H), 3.92 (3H), 6.22 (1H), 7.12 (1H), 7.18 (1H), 7.27 (1H), 7.63 (1H), 7.72 (1H), 7.75-7.81 (1H), 7.97 (1H), 8.24 (1H) ppm.

Intermediate Example 31a

4-{6-Bromo-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-*N*-cyclopropyl-2-methylbenzamide

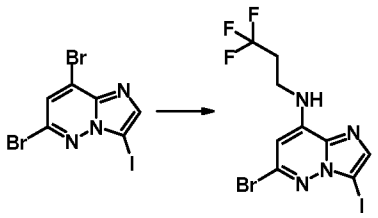


A mixture comprising 127 g (292 mmol) 6-bromo-3-iodo-*N*-(3,3,3-trifluoropropyl)imidazo[1,2-*b*]pyridazin-8-amine which was prepared according to intermediate example 31b, 95.93 g (438 mmol) [4-(cyclopropylcarbamoyl)-3-methylphenyl]boronic acid which was prepared according to intermediate example 31c, 23.8 g (29 mmol) (1,1,-bis(diphenylphosphino)ferrocene)-dichloropalladium (II), 438 mL aqueous 1M potassium carbonate solution and 973 mL tetrahydrofuran was stirred at 80°C for 8 hours and further 6 days at 60°C. Ethyl acetate was added to the separated organic phase and the mixture was washed with water. After filtration over ALLOX, the organic phase was evaporated and the residue was triturated with 200 mL EtOH to give 71.2 g (51%) of the title compound.

$^1$H-NMR (DMSO-d6): δ= 0.48-0.58 (2H), 0.63-0.73 (2H), 2.38 (3H), 2.68 (2H), 2.83 (1H), 3.61 (2H), 6.49 (1H), 7.40 (1H), 7.87 (1H), 7.93 (1H), 7.96-8.04 (2H), 8.32 (1H) ppm.

Intermediate Example 31b

6-Bromo-3-iodo-N-(3,3,3-trifluoropropyl)imidazo[1,2-*b*]pyridazin-8-amine

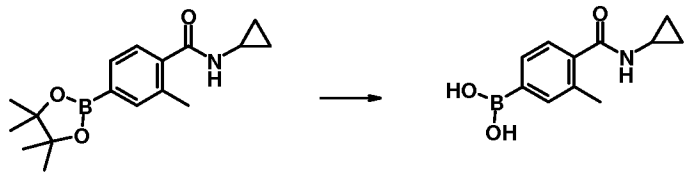


To a solution of 119 g 295 mmol) 6,8-dibromo-3-iodoimidazo[1,2-*b*]pyridazine which was prepared according to intermediate example 30e in 800 mL THF were added 66.8 g (590.8 mmol) 3,3,3-trifluoropropan-1-amine and the mixture was stirred at 80°c for 2 h and at 50°C overnight. The solution was evaporated, 600 mL ethyl acetate were added and the mixture was washed with water. The organic phase was dried and evaporated to give 127 g (99%) of the title compound.

$^1$H-NMR (DMSO-d6): δ= 2.63 (2H), 3.55 (2H), 6.43 (1H), 7.59 (1H), 7.89-7.98 (1H) ppm.

Intermediate Example 31c

[4-(cyclopropylcarbamoyl)-3-methylphenyl]boronic acid

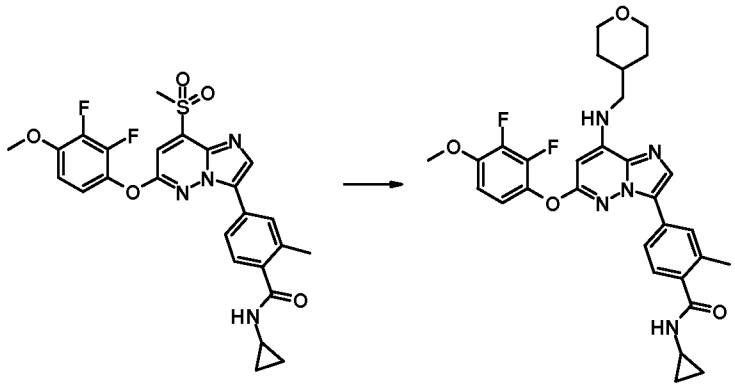


To a solution of N-cyclopropyl-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (20.2 g, 67.13 mol) which was prepared according to intermediate example 30i in acetone (300 mL) at rt was added sodium periodate (43.1 g, 201.40 mol) and ammonium acetate ( 134.26 mol, 134 mL 1M aqueous solution) and the mixture was stirred for 3h. More water was added (120 mL), and the mixture was stirred at 40°C for 2 h more. After addition of 4 N HCl (32 mL), the organic phase was removed in vaccuo and the reminder was extracted with ethyl actate. The organic phase was washed with sat. sodium chloride solution, filtered through a Whatman filter and evaporated. The residue was redissolved in toluene and evaporated ( two times) to yield 14.59 g (94.3 %) [4-(cyclopropylcarbamoyl)-3-

methylphenyl]boronic acid: $^1$H-NMR (300 MHz, $d_6$-DMSO): $\delta$ =8.21 (1H), 8.04 (2H), 7.56 (2H), 7.17 (1H), 2.77 (1H), 2.25 (3H), 0.62 (2H), 0.47 (2H) ppm.

**Example 32:**

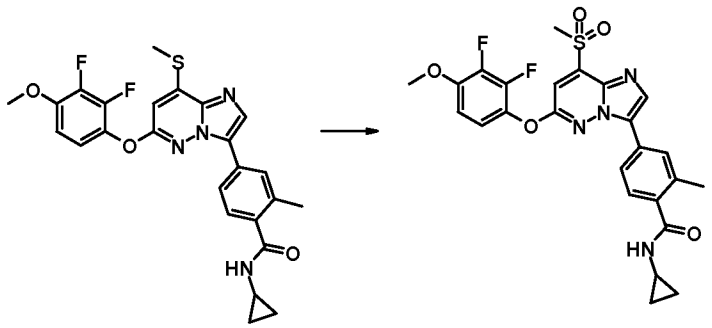
**N-cyclopropyl-4-{6-(2,3-difluoro-4-methoxyphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide**



To a solution of 52 mg (0.1 mmol) N-cyclopropyl-4-[6-(2,3-difluoro-4-methoxyphenoxy)-8-(methylsulfonyl)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide which was prepared according to intermediate example 32a in NMP (2 mL) at rt was 1-(tetrahydro-2H-pyran-4-yl)methanamine (35 mg, 0.3 mmol) and DIPEA (0.3 mmol, 51 µL) and the mixture was stirred at 110°C for 72 h to give after HPLC purification 26.9 mg (47%) of the title compound $^1$H-NMR (DMSO-d6): $\delta$= 0.43-0.50 (2H), 0.58-0.69 (2H), 1.22 (2H), 1.62 (2H), 1.86-2.02 (1H), 2.04-2.11 (3H), 2.77 (1H), 3.19-3.30 (4H), 3.82 (2H), 3.89 (3H), 6.16 (1H), 7.03-7.13 (1H), 7.15 (1H), 7.20-7.30 (1H), 7.57-7.63 (1H), 7.69 (1H), 7.80 (1H), 7.93 (1H), 8.24 (1H) ppm.

Intermediate Example 32a

N-cyclopropyl-4-[6-(2,3-difluoro-4-methoxyphenoxy)-8-(methylsulfonyl)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide

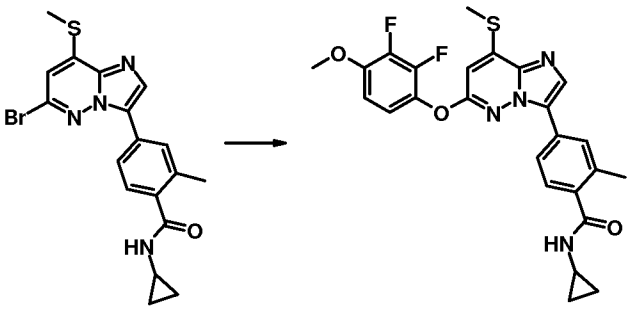


986 mg (1986 µmol) N-cyclopropyl-4-[6-(2,3-difluoro-4-methoxyphenoxy)-8-(methylsulfanyl)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide which was prepared according to intermediate example 32b were transformed in analogy to intermediate example 30b to give after working up 1040 mg (99%) of the title compound.

$^1$H-NMR (DMSO-d6): δ= 0.44-0.51 (2H), 0.61-0.69 (2H), 2.11 (3H), 2.73-2.84 (1H), 3.66 (3H), 3.91 (3H), 7.13-7.21 (1H), 7.23 (1H), 7.33-7.42 (1H), 7.64-7.70 (3H), 8.30 (1H), 8.40 (1H) ppm.

Intermediate Example 32b

N-cyclopropyl-4-[6-(2,3-difluoro-4-methoxyphenoxy)-8-(methylsulfanyl)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide



3.1 g (7428 µmol) 4-[6-bromo-8-(methylsulfanyl)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide which was prepared according to intermediate example 30b were transformed in analogy to example 31 using 2,3-difluoro-4-methoxyphenol to give after working up and purification 1010 mg (27%) of the title compound.

$^1$H-NMR (DMSO-d6): δ= 0.44-0.50 (2H), 0.59-0.70 (2H), 2.09 (3H), 2.67 (3H), 2.73-2.83 (1H), 3.90 (3H), 7.06 (1H), 7.14 (1H), 7.19 (1H), 7.31 (1H), 7.58-7.65 (1H), 7.67 (1H), 8.09 (1H), 8.26 (1H)ppm.

**Examples demonstrating the inhibitory effect on Mps-1 of preferred compounds A of the present invention**

**Biological assay: Proliferation Assay**

Cultivated tumour cells (MCF7, hormone dependent human mammary carcinoma cells, ATCC HTB22; NCI-H460, human non-small cell lung carcinoma cells, ATCC HTB-177; DU 145, hormone-independent human prostate carcinoma cells, ATCC HTB-81; HeLa-MaTu, human cervical carcinoma cells, EPO-GmbH, Berlin; HeLa-MaTu-ADR, multidrug-resistant human cervical carcinoma cells, EPO-GmbH, Berlin; HeLa human cervical tumour cells, ATCC CCL-2; B16F10 mouse melanoma cells, ATCC CRL-6475) were plated at a density of 5000 cells/well (MCF7, DU145, HeLa-MaTu-ADR), 3000 cells/well (NCI-H460, HeLa-MaTu, HeLa), or 1000 cells/well (B16F10) in a 96-well multititer plate in 200 µL of their respective growth medium supplemented 10% fetal calf serum. After 24 hours, the cells of one plate (zero-point plate) were stained with crystal violet (see below), while the medium of the other plates was replaced by fresh culture medium (200 µl), to which the test substances were added in various concentrations (0 µM, as well as in the range of 0.01-30 µM; the final concentration of the solvent dimethyl sulfoxide was 0.5%). The cells were incubated for 4 days in the presence of test substances. Cell proliferation was determined by staining the cells with crystal violet: the cells were fixed by adding 20 µl/measuring point of an 11% glutaric aldehyde solution for 15 minutes at room temperature. After three washing cycles of the fixed cells with water, the plates were dried at room temperature. The cells were stained by adding 100 µl/measuring point of a 0.1% crystal violet

solution (pH 3.0). After three washing cycles of the stained cells with water, the plates were dried at room temperature. The dye was dissolved by adding 100 µl/measuring point of a 10% acetic acid solution. The extinction was determined by photometry at a wavelength of 595 nm. The change of cell number, in percent, was calculated by normalization of the measured values to the extinction values of the zero-point plate (=0%) and the extinction of the untreated (0 µm) cells (=100%). The IC50 values were determined by means of a 4 parameter fit using the company's own software.

**Mps-1 kinase assay**

The human kinase Mps-1 phosphorylates a biotinylated substrate peptide. Detection of the phosphorylated product is achieved by time-resolved fluorescence resonance energy transfer (TR-FRET) from Europium-labelled anti-phospho-Serine/Threonine antibody as donor to streptavidin labelled with cross-linked allophycocyanin (SA-XLent) as acceptor. Compounds are tested for their inhibition of the kinase activity.

N-terminally GST-tagged human full length recombinant Mps-1 kinase (purchased from Invitrogen, Karslruhe, Germany, cat. no PV4071) was used. As substrate for the kinase reaction a biotinylated peptide of the amino-acid sequence PWDPDDADITEILG (C-terminus in amide form, purchased from Biosynthan GmbH, Berlin) was used.

For the assay 50 nL of a 100-fold concentrated solution of the test compound in DMSO was pipetted into a black low volume 384well microtiter plate (Greiner Bio-One, Frickenhausen, Germany), 2 µl of a solution of Mps-1 in assay buffer [0.1 mM sodium-ortho-vanadate, 10 mM $MgCl_2$, 2 mM DTT, 25 mM Hepes pH 7.7, 0.05% BSA, 0.001% Pluronic F-127] were added and the mixture was incubated for 15 min at 22°C to allow pre-binding of the test compounds to Mps-1 before the start of the kinase reaction. Then the kinase reaction was started by the addition of 3 µl of a solution of 16.7 adenosine-tri-phosphate

(ATP, 16.7 µM => final conc. in the 5 µl assay volume is 10 µM) and peptide substrate (1.67 µM => final conc. in the 5 µl assay volume is 1 µM) in assay buffer and the resulting mixture was incubated for a reaction time of 60 min at 22°C. The concentration of Mps-1 in the assay was adjusted to the activity of the enzyme lot and was chosen appropriate to have the assay in the linear range, typical enzyme concentrations were in the range of about 1 nM (final conc. in the 5 µl assay volume). The reaction was stopped by the addition of 3 µl of a solution of HTRF detection reagents (100 mM Hepes pH 7.4, 0.1% BSA, 40 mM EDTA, 140 nM Streptavidin-XLent [# 61GSTXLB, Fa. Cis Biointernational, Marcoule, France], 1.5 nM anti-phospho(Ser/Thr)-Europium-antibody [#AD0180, PerkinElmer LAS, Rodgau-Jügesheim, Germany].

The resulting mixture was incubated 1 h at 22°C to allow the binding of the phosphorylated peptide to the anti-phospho(Ser/Thr)-Europium-antibody. Subsequently the amount of phosphorylated substrate was evaluated by measurement of the resonance energy transfer from the Europium-labelled anti-phospho(Ser/Thr) antibody to the Streptavidin-XLent. Therefore, the fluorescence emissions at 620 nm and 665 nm after excitation at 350 nm was measured in a Viewlux TR-FRET reader (PerkinElmer LAS, Rodgau-Jügesheim, Germany). The "blank-corrected normalized ratio" ( a Viewlux specific readout, similar to the traditional ratio of the emissions at 665 nm and at 622 nm, in which blank and Eu-donor crosstalk are subtracted from the 665 nm signal before the ratio is calculated) was taken as the measure for the amount of phosphorylated substrate. The data were normalised (enzyme reaction without inhibitor = 0 % inhibition, all other assay components but no enzyme = 100 % inhibition). Test compounds were tested on the same microtiter plate at 10 different concentrations in the range of 20 µM to 1 nM (20 µM, 6.7 µM, 2.2 µM, 0.74 µM, 0.25 µM, 82 nM, 27 nM, 9.2 nM, 3.1 nM and 1 nM, dilution series prepared before the assay at the level of the 100fold conc. stock solutions by serial 1:3 dilutions) in duplicate values for each concentration and $IC_{50}$ values were calculated by a 4 parameter fit using an in-house software.

**Table 1**

| Example | Mps-1 IC50 [nM] |
|---|---|
| 1 | 0.4 |
| 2 | 0.6 |
| 3 | 0.2 |
| 4 | 0.3 |
| 5 | 0.7 |
| 6 | 0.7 |
| 7 | 0.5 |
| 8 | 0.8 |
| 9 | 1.2 |
| 10 | 0.5 |
| 11 | 0.3 |
| 12 | 0.6 |

**Table 1 (cont.)**

| Example | Mps-1 IC50 [nM] |
|---|---|
| 13 | 0.4 |
| 14 | 0.6 |
| 15 | 0.4 |
| 16 | 0.6 |
| 17 | 0.7 |
| 18 | 1.5 |
| 19 | 0.6 |
| 20 | 0.8 |
| 21 | 0.5 |
| 22 | 0.4 |
| 23 | 0.4 |
| 24 | 0.3 |
| 25 | 0.9 |

**Spindle Assembly Checkpoint Assay**

The spindle assembly checkpoint assures the proper segregation of chromosomes during mitosis. Upon entry into mitosis, chromosomes begin to condensate which is accompanied by the phosphorylation of histone H3 on serine 10. Dephosphorylation of histone H3 on serine 10 begins in anaphase and ends at early telophase. Accordingly, phosphorylation of histone H3 on serine 10 can be utilized as a marker of cells in mitosis. Nocodazole is a microtubule destabilizing substance. Thus, nocodazole interferes with microtubule dynamics and mobilises the spindle assembly checkpoint. The cells arrest in mitosis at G2/M transition and exhibit phosphorylated histone H3 on serine 10. An inhibition of the spindle assembly checkpoint by Mps-1 inhibitors overrides the mitotic blockage in the presence of nocodazole, and the cells complete mitosis prematurely. This alteration is detected by the decrease of cells with phosphorylation of histone H3 on serine 10. This decline

is used as a marker to determine the capability of compounds of the present invention to induce a mitotic breakthrough.

Cultivated cells of the human cervical tumour cell line HeLa (ATCC CCL-2) were plated at a density of 2500 cells/well in a 384-well microtiter plate in 20 µl Dulbeco's Medium (w/o phenol red, w/o sodium pyruvate, w 1000 mg/ml glucose, w pyridoxine) supplemented with 1% (v/v) glutamine, 1% (v/v) penicillin, 1% (v/v) streptomycin and 10% (v/v) fetal calf serum. After incubation overnight at 37°C, 10 µl/well nocodazole at a final concentration of 0.1 µg/ml were added to cells. After 24 h incubation, cells were arrested at G2/M phase of the cell cycle progression. Test compounds solubilised in dimethyl sulfoxide (DMSO) were added at various concentrations (0 µM, as well as in the range of 0.005 µM - 10 µM; the final concentration of the solvent DMSO was 0.5% (v/v)). Cells were incubated for 4 h at 37°C in the presence of test compounds. Thereafter, cells were fixed in 4% (v/v) paraformaldehyde in phosphate buffered saline (PBS) at 4°C overnight then permeabilised in 0.1% (v/v) Triton X™ 100 in PBS at room temperature for 20 min and blocked in 0.5% (v/v) bovine serum albumin (BSA) in PBS at room temperature for 15 min. After washing with PBS, 20 µl/well antibody solution (anti-phospho-histone H3 clone 3H10, FITC; Upstate, Cat# 16-222; 1:200 dilution) was added to cells, which were incubated for 2 h at room temperature. Afterwards, cells were washed with PBS and 20 µl/well HOECHST 33342 dye solution (5 µg/ml) was added to cells and cells were incubated 12 min at room temperature in the dark. Cells were washed twice with PBS then covered with PBS and stored at 4°C until analysis. Images were acquired with a Perkin Elmer OPERA™ High-Content Analysis reader. Images were analyzed with image analysis software MetaXpress™ from Molecular devices utilizing the Cell Cycle application module. In this assay both labels HOECHST 33342 and phosphorylated Histone H3 on serine 10 were measured. HOECHST 33342 labels DNA and is used to count cell number. The staining of phosphorylated Histone H3 on serine 10 determines the number of mitotic cells. Inhibition of Mps-1

decreases the number of mitotic cells in the presence of nocodazole indicating an inappropriate mitotic progression. The raw assay data were further analysed by four parameter logistic regression analysis to determine the $IC_{50}$ value for each tested compound.

It will be apparent to persons skilled in the art that assays for other Mps kinases may be performed in analogy using the appropriate reagents.

**Investigation of *in vitro* metabolic stability in rat hepatocytes (**including calculation of hepatic *in vivo* blood clearance (CL))

Hepatocytes from Han Wistar rats were isolated via a 2-step perfusion method. After perfusion, the liver was carefully removed from the rat: the liver capsule was opened and the hepatocytes were gently shaken out into a Petri dish with ice-cold WME. The resulting cell suspension was filtered through sterile gaze in 50 ml falcon tubes and centrifuged at 50 × *g* for 3 min at room temperature. The cell pellet was resuspended in 30 ml WME and centrifuged through a Percoll® gradient for 2 times at 100 × *g*. The hepatocytes were washed again with Williams' medium E (WME) and resuspended in medium containing 5% FCS. Cell viability was determined by trypan blue exclusion.

For the metabolic stability assay liver cells were distributed in WME containing 5% FCS to glas vials at a density of $1.0 \times 10^6$ vital cells/ml. The test compound was added to a final concentration of 1 µM. During incubation, the hepatocyte suspensions were continuously shaken and aliquots were taken at 2, 8, 16, 30, 45 and 90 min, to which equal volumes of cold methanol were immediately added. Samples were frozen at -20° C over night, after subsequently centrifuged for 15 minutes at 3000 rpm and the supernatant was analyzed with an Agilent 1200 HPLC-system with LCMS/MS detection.

The half-life of a test compound was determined from the concentration-time plot. From the half-life the intrinsic clearances were calculated. Together

with the additional parameters liver blood flow, amount of liver cells *in vivo* and *in vitro*. The hepatic *in vivo* blood clearance (CL) and the maximal oral bioavailability ($F_{max}$) was calculated. The following parameter values were used: Liver blood flow – 4.2 L/h/kg rat; specific liver weight – 32 g/kg rat body weight; liver cells *in vivo*- 1.1 x $10^8$ cells/g liver, liver cells *in vitro* – 0.5 x $10^6$/ml.

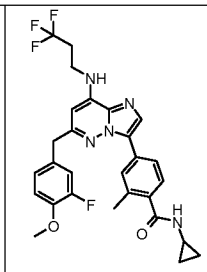
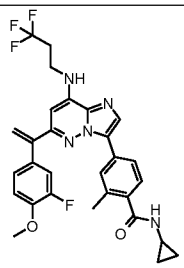
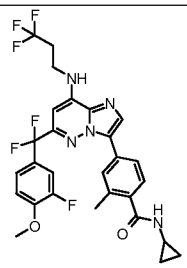
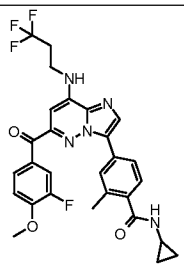
Tables 2, 3, 4, 5 and 6 compare the *in vitro* metabolic stability in rat hepatocytes expressed as hepatic *in vivo* blood clearance (CL) and the maximal oral bioavailability ($F_{max}$) for three sets of compounds.

Each set comprises a comparative compound bearing a -$CH_2$-$R^{3c}$-group for $R^3$ that is compared with two compounds bearing a -$C(R^{3a})(R^{3b})$-$R^{3c}$-group.

The remaining substitution pattern in each set is conserved to allow an assessment of the influence of $R^{3a}$ and $R^{3b}$ on the hepatic *in vivo* blood clearance and the maximal oral bioavailability.

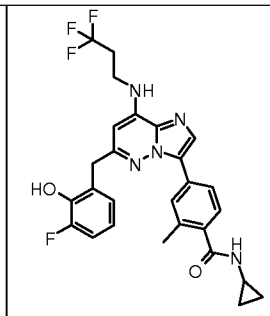
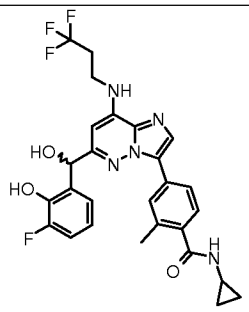
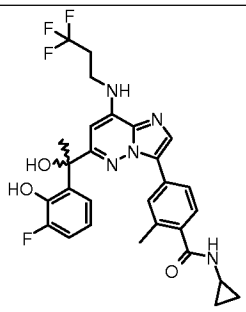
The set of compounds given in Table 2 clearly indicate an improved hepatic *in vivo* blood clearance and an improved maximal oral bioavailability if both $R^{3a}$ and $R^{3b}$ do not represent a hydrogen atom.

**Table 2**

| |  |  |  |  |
|---|---|---|---|---|
| Example | Example 0.1 | Example 1 | Example 2 | Example 13 |
| $F_{max}$ [%] | 29 | 39 | 64 | 75 |
| CL [L/h/kg] | 3.0 | 2.6 | 1.5 | 1.1 |

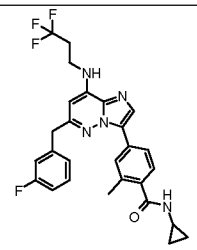
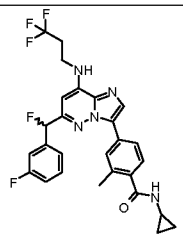
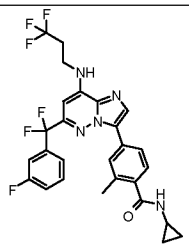
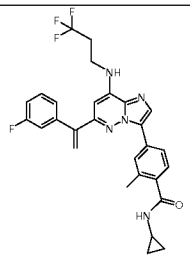
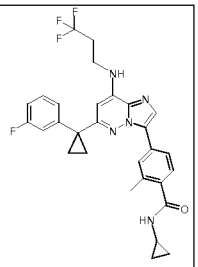
The set of compounds given in Table 3 clearly indicate an improved hepatic *in vivo* blood clearance and an improved maximal oral bioavailability if at least one of $R^{3a}$ and $R^{3b}$ does not represent a hydrogen atom.

**Table 3**

| |  |  |  |
|---|---|---|---|
| Example | Example 0.2 | Example 3 | Example 4 |
| $F_{max}$ [%] | 3 | 18 | 36 |
| CL [L/h/kg] | 4.1 | 3.4 | 2.7 |

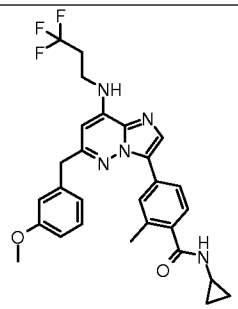
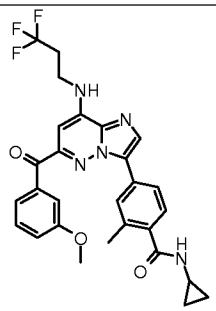
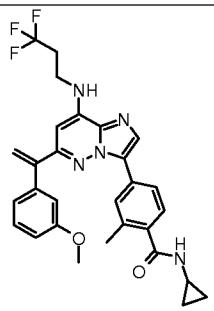
The set of compounds given in Table 4 clearly indicate an improved hepatic *in vivo* blood clearance and an improved maximal oral bioavailability if at least one of $R^{3a}$ and $R^{3b}$ does not represent a hydrogen atom.

**Table 4**

| |  |  |  |  |  |
|---|---|---|---|---|---|
| Example | Example 0.3 | Example 5 | Example 6 | Example 24 | Example 25 |
| $F_{max}$ [%] | 43 | 49 | 70 | 48 | 52 |
| CL [L/h/kg] | 2.4 | 2.1 | 1.3 | 2.2 | 2.0 |

The set of compounds given in Table 5 clearly indicate an improved hepatic *in vivo* blood clearance and an improved maximal oral bioavailability if both $R^{3a}$ and $R^{3b}$ do not represent a hydrogen atom.

**Table 5**

| |  |  |  |
|---|---|---|---|
| Example | Example 0.4 | Example 7 | Example 8 |
| $F_{max}$ [%] | 18 | 26 | 57 |
| CL [L/h/kg] | 3.4 | 3.1 | 1.8 |

The set of compounds given in Table 6 clearly indicate an improved hepatic *in vivo* blood clearance and an improved maximal oral bioavailability if both $R^{3a}$ and $R^{3b}$ do not represent a hydrogen atom.

**Table 6**

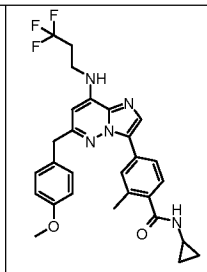
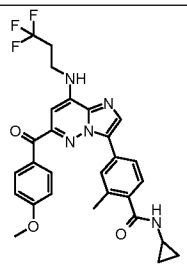
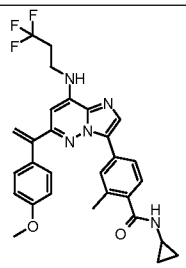
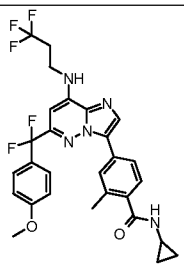
| |  |  |  |  |
|---|---|---|---|---|
| Example | Example 0.5 | Example 9 | Example 10 | Example 16 |
| $F_{max}$ [%] | 35 | 71 | 48 | 56 |
| CL [L/h/kg] | 2.7 | 1.2 | 2.2 | 1.9 |

Table 7 lists hepatic *in vivo* blood clearance and the maximal oral bioavailability of additional compounds for which both, $R^{3a}$ and $R^{3b}$, do not represent a hydrogen atom.

**Table 7**

| Example | $F_{max}$ [%] | CL [L/h/kg] |
|---|---|---|
| 11 | 45 | 2.3 |
| 12 | 67 | 1.4 |
| 14 | 51 | 2.1 |
| 15 | 53 | 2.0 |
| 17 | 50 | 2.1 |
| 18 | 76 | 1.0 |
| 22 | 28 | 3.0 |
| 23 | 40 | 2.5 |

The data given in Tables 2, 3, 4, 5, 6 and 7 clearly indicate that the hepatic *in vivo* blood clearance as well as the maximal oral bioavailability of the whole molecule can be surprisingly improved if at least one of $R^{3a}$ and $R^{3b}$ does not represent a hydrogen atom.

**Determination of Inhibitory Potential on Human CYP3A4**

The potential of the test compound to act as a competitive inhibitor of CYP3A4 was evaluated in in vitro assays, using human liver microsomes and the reference substrate midazolam. The test compound was solved in acetonitrile. Human liver microsomal preparation (pool of HLM) was applied for the assay.

A stock solution of the test compound was added to phosphate buffer containing EDTA, NADP, glucose 6-phosphate, and glucose 6-phosphate dehydrogenase. This mixture was sequentially diluted on a Genesis Workstation (Tecan, Crailsheim, FRG). After pre-warming, reaction was initiated by addition of a mixture of probe substrate (midazolam). Finally, the incubation mixtures contained human liver microsomes at protein concentration of 60 µg/mL, NADPH-regenerating system (1 mM NADP, 5.0 mM glucose 6-phosphate, glucose 6-phosphate dehydrogenase (1.5 U/mL), 1.0 mM EDTA, the test compound at 6 different concentrations, 2.5µM midazolam as probe substrate, and phosphate buffer (50 mM, pH 7.4) in a total volume of 200 µL. Incubations were performed on a Genesis Workstation (Tecan, Crailsheim, FRG) in 96-well plates (Microtiter plate, 96-well plate) at 37°C. Stock solution of probe substrate was prepared in water (midazolam 10 mM). Ketoconazole was used as positive control of a direct-acting inhibitor. The reference samples (substrate, but no inhibitor) were incubated in parallel in sextuple and contained the same amount of solvent as the test incubations. Reactions were stopped by addition of 100 µL acetonitrile containing the internal standard. Precipitated proteins were removed by centrifugation of the well plate, supernatants were analyzed by LC-MS/MS.

The CYP3A4-mediated metabolic activity in the presence of the test compounds was expressed as percentages of the corresponding reference value. A sigmoid-shaped curve was fitted to the data to calculate the enzyme inhibition parameter IC50 using a nonlinear least-squares regression analysis of the plot of percent control activity versus concentration of the test inhibitor. Observing less than 50% inhibition, the data were not extrapolated; hence, IC50 were reported as being greater than the highest concentration of the test compound applied.

The set of compounds given in Table 8 surprisingly exhibits a superior overall profile with respect to Mps-related activity in a functional assay (Spindle Assembly Checkpoint Assay), antiproliferative activity (Proliferation Assay with HeLa cells), metabolic stability (in vitro metabolic stability in rat hepatocytes) and drug-drug interaction potential (inhibition of liver enzyme CYP3A4). Selection criteria were Activity in Spindle Assembly Checkpoint Assay < 1.0 nM, Activity in Proliferation Assay with HeLa cells < 25 nM, in vitro metabolic stability in rat hepatocytes Fmax ≥ 39% and inhibition of liver enzyme CYP3A4 ≥ 5 µM.

**Table 8**

| Example | SAC [nM] | HeLa [nM] | Fmax rat hep [%] | CYP3A4 [µM] |
|---|---|---|---|---|
| 30 | 0.97 | 2.9 | 44 | 5 |
| 31 | 0.62 | 7.8 | 72 | 10 |
| 32 | 0.08 | 18.1 | 39 | 10 |

**Examples demonstrating the synergistic effect of the combinations of compounds A and B of the present invention**

**Cell lines and culture conditions:**

Unless otherwise indicated, media and supplements for cell culture were purchased from Gibco-Life Technologies Corporation (Carlsbad, CA, USA) and plastic ware from Corning B.V. Life Sciences (Corning, NY, USA). Wild type, *Bax*$^{-/-}$ and *TP53*$^{-/-}$ human colon carcinoma HCT 116 cells (kindly provided by Bert Vogelstein, Johns Hopkins Kimmel Cancer Center, Baltimore, MD, USA) were routinely maintained in McCoy's 5A medium supplemented with 10% fetal calf serum (FCS), 10 mM HEPES buffer, 100 units/mL penicillin G sodium and 100 µg/mL streptomycin sulfate. Wild type, *Bak*$^{-/-}$ and *Bak*$^{-/-}$*Bax*$^{-/-}$ mouse embryonic fibroblasts MEFs cells were routinely maintained in DMEM medium supplemented with 10% fetal calf serum (FCS), 10 mM HEPES buffer, 100 units/mL penicillin G sodium, 100 µg/mL streptomycin sulfate and non essential amino acids. Cells were seeded onto the appropriate supports (6-, 12-, 24- or 96-well plates) 24 h before the beginning of experiments.

**Chemicals:**

The pan-caspase inhibitor Z-VAD-fmk (*N*-benzyloxycarbonyl-Val-Ala-Asp.fluoromethylketone) was obtained from Bachem Bioscience (Bubendorf, Switzerland) and stocked as a 50 mM solution in DMF. *Cis*-diammineplatinum(II) dichloride (cisplatin, CDDP) and anthra [1,9-cd] pyrazole-6 (2H)-one (SP600125) were purchased from Sigma-Aldrich (St Louis, MO, USA). The Bcl-2 inhibitor ABT-737 was purchased from Selleckchem.com and a stock solution of 100 mM in DMSO was prepared. An appropriate volume of DMSO and/or DMF was always employed to provide negative control conditions.

**Cytofluorometric studies:**

For the simultaneous quantification of plasma membrane integrity and mitochondrial transmembrane potential ($\Delta\Psi_m$), cells were collected and stained with 1 µg/mL propidium iodide (PI, which only incorporates into dead cells, from Sigma-Aldrich) and 40 nM 3,3'-dihexyloxacarbocyanine iodide ($DiOC_6(3)$, a $\Delta\psi_m$-sensitive dye, from Molecular Probes-Invitrogen, Eugene, OR, USA) for 30 min at 37 °C [Galluzzi et al. Cell Death Differentiation 2009, 16, 1093-1107; Kepp et al. Nat. Rev. Drug Discovery 2011, 10, 221-237]. For the assessment of cell cycle distribution, cells were collected, washed once with 0.1% (w/v) D-glucose (Sigma-Aldrich) in PBS, and then fixed by gentle vortexing in ice-cold 80% (v/v) ethanol (Carlo Erba Reagents, Milano, Italy) for 30 sec. After overnight incubation at -20 °C, samples were centrifuged to remove ethanol and stained with 50 µg/mL PI in 0.1% (w/v) D-glucose in PBS supplemented with 1 µg/mL (w/v) RNAse A (Sigma-Aldrich) for 30 min at 37°C. Afterwards, samples were incubated for at least 2 h at 4 °C before cytofluorometric analysis. For the EdU assay, cells were incubated with 10 µM EdU for 30 min at 37°C, fixed, permeabilized and stained with the fluorescent dye azide (Click-iT™ reaction cocktail, from Invitrogen) and PI, according to the manufacturer's instructions. Cytofluorometric acquisitions were performed by means of a FACSCalibur (BD Biosciences, San Diego, CA, USA) or a FACScan (BD Biosciences) cytofluorometer equipped with a 70 µm nozzle or with a Gallios cytofluorometer (Beckman Coulter, Miami, FL, USA). Data were statistically evaluated using the CellQuest™ (Becton Dickinson) or Kaluza (Beckman Coulter) software. Only the events characterized by normal forward scatter (FSC) and side scatter (SSC) parameters were gated for inclusion in the statistical analysis.

**RNA interference:**

The knockdown of proteins reported in **Table 4S** was performed with validated specific small interfering RNAs (siRNA) purchased from Sigma-Proligo. Alternatively, siRNA duplexes for the downregulation of AURKA (SIHK0142)

were purchased from Sigma-Aldrich and siRNAs for the downregulation of BAK1 and BAX (Hs_BAK1_5 and Hs_BAX_10 HP Validated siRNAs, respectively) from Qiagen (Hilden, Germany). Cells pre-seeded in 12-well plates were transfected with siRNAs at 30-40% confluence by means of the HiPerFect® transfection reagent (Qiagen), as previously described. After 48 or 72 h, transfection efficiency was determined by immunoblotting.

## Table 4S: siRNAs sequences

| Target | Sequence | Reference |
|---|---|---|
| UNR | 5' GCCGGUAUGCCGGUUAAGU 3' | |
| APAF-1 | 5' GAGCAGCUAUGCUGAUUAA 3' | (Zermati et al 2007) |
| APC | 5' GGAAGUAUUGAAGAUGAAG 3' | (Huang and Guo 2006) |
| ATM | 5' AACAUACUACUCAAAGACA 3' | (Olson et al 2006) |
| ATR | 5' CCUCCGUGAUGUUGCUUGA 3' | (Myers and Cortez 2006) |
| BAK1 | Hs_BAK1_5 (Qiagen) | (de La Motte Rouge et al |
| BAX | Hs_BAX_10 (Qiagen) | (de La Motte Rouge et al |
| BCL2 | 5'-GCUGCACCUGACGCCCUUC-3' | (Maley et al 2004) |
| BCL2XL | 5' CAGGGACAGCAUAUCAGAG 3' | (Jiang and Milner 2003) |
| BECN1 | 5' GAUUGAAGACACAGGAGGC 3' | (Boya et al 2005) |
| BRCA1 | 5' GCAACCUGUCUCCACAAAG 3' | (Lou et al 2003) |
| BRCA2 | 5' CUGAGCAAGCCUCAGUCAA 3' | (Fan et al 2006) |
| BUB1 | 5'AUACCACAAUGACCCAAGA 3' | (Johnson et al 2004) |
| BUBR1 | 5' AAGGGAAGCCGAGCUGUUGAC 3' | (Wang et al 2004) |
| CENPE | 5' GGCUACAAUGGUACUAUAU 3' | (Johnson et al 2004) |
| CHK1 | 5' UCGUGAGCGUUUGUUGAAC 3' | (Pichierri and Rosselli 2004) |
| CHK2 | 5' UGUGUGAAUGACAACUACU 3' | (Vitale et al 2007) |
| CLIP1 | 5' CUGCAAUGACGACGAAACC 3' | (Tanenbaum et al 2006) |
| HSET | Smart-pool L-004958 (Dharmacon) | (Vitale et al 2010) |
| LKB1 | 5' GGACUGACGUGUAGAACAA 3' | (Zhong et al 2008) |
| MAD2 | 5' ACCUUUACUCGAGUGCAGA 3' | (Nitta et al 2004) |
| MCL1 | 5' CGGGACUGGCUAGUUAAACAA 3' | (Kepp et al 2009) |
| MOS | 5' GCCCGCGAACAUCUUGAUC 3' | (Vitale et al 2010) |
| MPS1 (1) | 5' CCCAGAGGACUGGUUGAGU 3' | (Stucke et al 2004) |
| MPS1 (2) | 5' GCACGUGACUACUUUCAAA 3' | (Xu et al 2009) |
| p14ARF | 5' GCUUCCUAGAAGACCAGGU 3' | (Ma and Pederson 2007) |
| p15INK4b | 5' GGGAUAUUUAGGAGUGUGU 3' | (Chen et al 2006) |
| p16INK4a | 5' CGCACCGAAUAGUUACGGU 3' | (Gabriely et al 2011) |
| p21 | 5' CUUCGACUUUGUCACCGAG 3' | (Spierings et al 2004) |
| p38□ | 5' GCAAGAAACUAUAUUCAG 3' | (Gao et al 2004) |
| p53 | 5' GACUCCAGUGGUAAUCUAC 3' | (Brummelkamp et al 2002) |
| p63 | 5' CCAUGAGCUGAGCCGUGAA 3' | (Lee et al 2006) |
| p73 | 5' ACGUCCAUGCUGGAAUCCG 3' | (Toscano et al 2007) |
| PAWR | Smart-pool M-004434 (Dharmacon) | |
| PLK1 | 5' CGAGCUGCUUAAUGACGAG 3' | (Gimenez-Abian et al 2004) |
| PLK4 | 5' GCCAUGUACAAAGCAGGAA 3' | (Li et al 2005) |
| PTEN | 5' GUCAGAGGCGCUAUGUGUA 3' | (Rottmann et al 2008) |
| TNKS | 5' CAAUUCACCGUCGUCCUCU 3' | (Chang et al 2005) |
| UVRAG | 5' CAUCAGCUCCUUGAUACCUACUUUA 3' | (Itakura et al 2008) |
| VDAC1 | 5' GUACGGCCUGACGUUUACA 3' | (Criollo et al 2007) |

**Results:**

HCT116 and MEF cells were transfected with 36 distinct siRNAs that target cell cycle or cell death-relevant genes/proteins. Among this collection, three siRNAs that deplete one of the three anti-apoptotic multidomain proteins of the Bcl-2 family (Bcl-2, Bcl-$X_L$, Mcl-1) were found to be particularly efficient in sensitizing the cells to BAY 2 or BAY 3-induced killing (**Fig. 1A**). Conversely, siRNAs targeting either of the two pro-apoptotic multidomain proteins of the Bcl-2 family (Bax, Bak) avoided the loss of cellular viability induced by BAY 2 or BAY 3 (**Fig. 1A**).

Moreover, depletion of Apaf-1, the essential co-activator of caspase-9 acting downstream of mitochondria (Galluzzi et al), protected against killing by Mps-1 inhibition. Accordingly, the knockout of Bax, Bak or both greatly reduced cell killing by BAY 2 and BAY 3 (**Fig. 1B,C**), and neutralization of Bcl-2 and Bcl-XL with ABT737 sensitized to cell death induction by BAY 2 and BAY 3 (**Fig. 1D**). The proteins of the Bcl-2 family are known to regulate apoptosis through their capacity to regulate mitochondrial membrane permeabilization and caspase activation [Kroemer et al. Phys. Rev. 2007, 87, 99-163]. Accordingly, BAY 2 and 3 induced the release of cytochrome *c* from mitochondria to cytosol, preceding the activation of caspase-3 (**Fig. 1E**), and inhibition of caspases by Z-VAD-fmk reduced killing by BAY 2 or BAY 3 (**Fig. 1F**).

## Description of the Figures

**Figures 1A to 1F:** Depletion or pharmacological inhibition of anti-apoptotic proteins of the Bcl-2 family sensitizes tumor cells to MPS1 inhibitors BAY 2 and BAY 3.

**Fig 1A:** Human colorectal carcinoma HCT116 cells transfected with a control siRNA (siUNR) or with a panel of validated siRNAs directed against the reported proteins were treated 24h later with 1 μM BAY 2 or BAY 3 for

additional 48 h. Thereafter apoptosis-associated parameters were assessed by co-staining with $DiOC_6(3)$/PI and cytofluorimetric analyses. The figure reports the unsupervised hierarchical clustering of the effects of the siRNA screen on the response to the drugs. Green and red boxes depict siRNA-mediated cytoprotection ($\Delta < 0$) and chemosensitization ($\Delta > 0$), respectively. $\Delta$ represents the difference between the percentage of death in cell transfected with the reported siRNAs then left untreated or treated with BAY 2 or BAY 3 and the percentage of apoptosis in siUNR-transfected cells in the same condition.

**Figs. 1B -1D:** HCT116 cells or immortalized MEFs with the illustrated genetic background, as well as WT HCT116 pre-exposed for 3h to the Bcl-2/Bcl-$X_L$ inhibitor ABT-737, were kept in control conditions or incubated for 72 h with BAY 2 or BAY 3 at the depicted dose (usually 1 μM). Thereafter, cell were collected and analyzed by $DiOC_6(3)$/PI co-staining.

**Fig. 1E:** BAY 2- or BAY 3- treated HCT 116 cells were co-immunostained with antibodies directed against cytochrome *c* (CYT *C*) and activated caspase-3 (CASP3a) followed by quantification of the percentage of cells presenting exhibiting diffuse CYT *C* staining or caspase-3 activation as determined by fluorescence microscopy. Nuclei were counterstained with Hoechst 33342. Representative fluorescence microphotographs of HCT116 cells treated with 1 μM BAY 2 for 72 h and quantitative results at (means ± SEM, $n = 4$) are shown. Scale bar = 10 μm.

**Fig. 1F:** Upon 24 h of pre-treatment with the pancaspase inhibitor Z-VAD-FMK, HCT 116 cells were subjected to BAY 2 or BAY 3 administration followed by cytofluorometric assessment of cell death-related parameters as described in panel **B-D**. Means ± SEM; $n = 4$.

In Fig.s **1B**, **1C**, **1D** and **1F**, white and black columns illustrate the percentage of dying ($PI^-$ $DiOC_6(3)^{low}$) and dead ($PI^+$) cells, respectively (means ± SEM, $n = 3$).

**Conclusions:**

The depletion or pharmacological inhibition of the anti-apoptotic proteins of the Bcl-2 family, such as Bcl-2, Bcl-$X_L$, Mcl-1 sensitized to Mps-1 inhibitors, while the depletion of the pro- apoptotic proteins Bax and Bak reduced Mps-1 inhibitor-mediated killing of tumor cells. These results suggest that combination treatment of tumor cells with inhibitors of anti-apoptotic proteins of the Bcl-2 family and Mps-1 inhibitors has superior therapeutic efficacy as compared to the respective single agent treatments.

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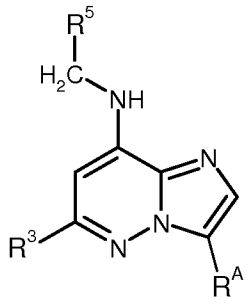
## CLAIMS

**1.** Combination of at least two compounds A and B, compound A being an inhibitor of Mps-1 kinase, and compound B being an inhibitor of an anti-apoptotic protein of the Bcl-2 family.

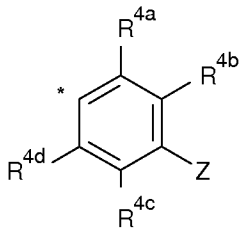
**2.** The combination according to claim 1, wherein the compound A is selected from the group of compounds of general formula (I) :



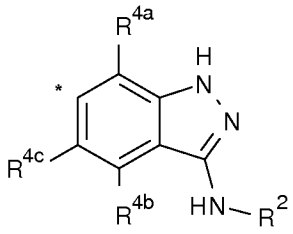
(I)

in which :

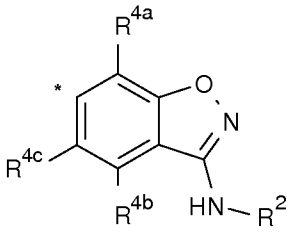
$R^A$ represents a



or



or



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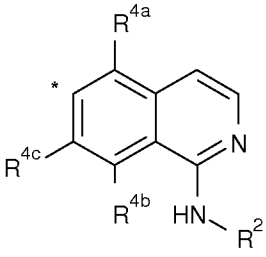
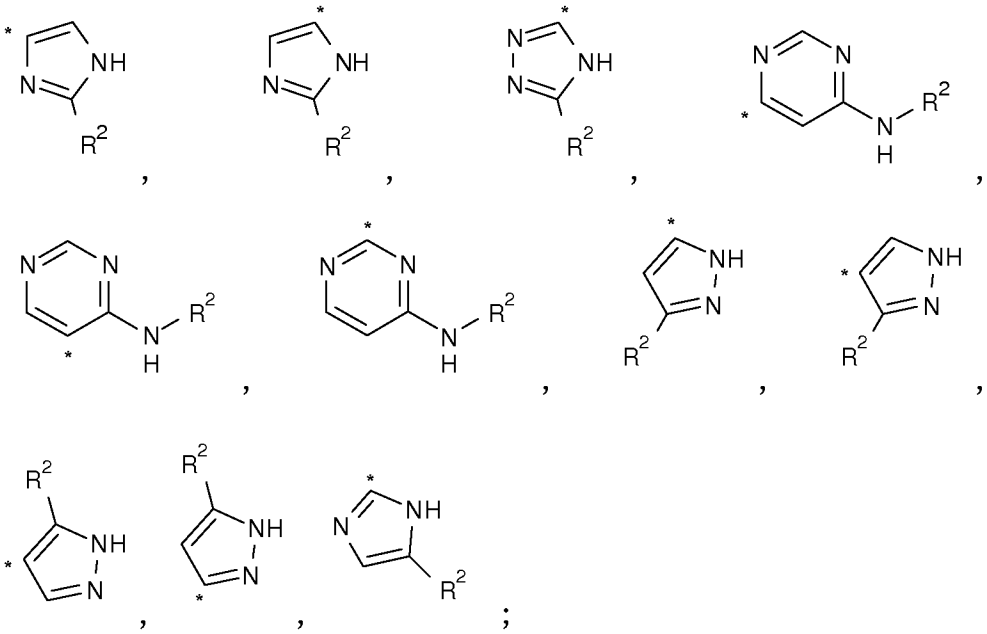


-group ;

wherein * indicates the point of attachment of said groups with the rest of the molecule ;

Z represents a -C(=O)N(H)$R^2$ or -C(=S)N(H)$R^2$ group, or a group selected from



wherein * indicates the point of attachment of said groups with the rest of the molecule ;

$R^2$ represents a hydrogen atom, or a $C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})N$-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, -$C_1$-$C_6$-alkyl-CN, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, $C_2$-$C_6$-alkenyl-, $C_2$-$C_6$-alkynyl- or $C_3$-$C_6$-cycloalkyl- group ;
wherein said $C_3$-$C_6$-cycloalkyl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 groups selected from: halogen, -OH, -CN, $C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy-, halo-$C_1$-$C_6$-alkyl-;

$R^3$ represents a hydrogen atom or a halogen atom, or a -CN, $C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy-, -$(CH_2)_m$-$C_2$-$C_6$-alkenyl, -$(CH_2)_m$-$C_4$-$C_8$-cycloalkenyl, -$(CH_2)_m$-$C_2$-$C_6$-alkynyl, -$(CH_2)_m$-$C_3$-$C_6$-cycloalkyl, -$(CH_2)_m$-(3- to

7-membered heterocycloalkyl), -$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-$C_1$-$C_6$-alkyl-, heteroaryl-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})$N-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, $C_3$-$C_6$-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, $C_2$-$C_6$-alkenyl-, $C_4$-$C_8$-cycloalkenyl-, $C_2$-$C_6$-alkynyl-, aryl-, -$C_1$-$C_6$-alkyl-aryl, -$C_1$-$C_6$-alkyl-heteroaryl, heteroaryl-, $C_1$-$C_6$-alkyl-X-, -X-$(CH_2)_m$-$C_2$-$C_6$-alkenyl, -X-$(CH_2)_m$-$C_4$-$C_8$-cycloalkenyl, -X-$(CH_2)_m$-$C_2$-$C_6$-alkynyl, -X-$(CH_2)_m$-$C_3$-$C_6$-cycloalkyl, -X-$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -X-$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-X-, heteroaryl-X-, -C(=O)$R^6$, -C(=O)N(H)$R^{6a}$, -C(=O)N($R^{6a}$)$R^{6b}$, -C(=O)O-$R^6$, -N($R^{6a}$)$R^{6b}$, -$NO_2$, -N(H)C(=O)$R^6$, -O$R^6$, -S$R^6$, -S(=O)$R^6$, -S(=O)$_2R^6$, -S(=O)(=N$R^{6a}$)$R^{6b}$, -S(=O)$_2$N($R^{6b}$)$R^{6c}$, -S-$(CH_2)_n$-N($R^{6a}$)$R^{6b}$ or -S-$(CH_2)_n$-(3- to 7-membered heterocycloalkyl) group ;

wherein said $C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy-, -$(CH_2)_m$-$C_2$-$C_6$-alkenyl, -$(CH_2)_m$-$C_2$-$C_6$-alkynyl, -$(CH_2)_m$-$C_3$-$C_6$-cycloalkyl, aryl-$C_1$-$C_6$-alkyl-, heteroaryl-$C_1$-$C_6$-alkyl-, $C_3$-$C_6$-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, $C_2$-$C_6$-alkenyl-, $C_4$-$C_8$-cycloalkenyl-, $C_2$-$C_6$-alkynyl-, aryl-, $C_1$-$C_6$-alkyl-X-, -X-$(CH_2)_m$-$C_2$-$C_6$-alkenyl, -X-$(CH_2)_m$-$C_4$-$C_8$-cycloalkenyl, -X-$(CH_2)_m$-$C_2$-$C_6$-alkynyl, -X-$(CH_2)_m$-$C_3$-$C_6$-cycloalkyl, -X-$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), -X-$(CH_2)_m$-(4- to 8-membered heterocycloalkenyl), aryl-X-, heteroaryl-X-, -$C_1$-$C_6$-alkyl-aryl, -$C_1$-$C_6$-alkyl-heteroaryl or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3, 4 or 5 $R^7$ groups ;

$R^{4a}$, $R^{4b}$, $R^{4c}$, $R^{4d}$

represent, independently from each other, a hydrogen or halogen atom, or a -CN, $C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})$N-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, -C(=O)$R^6$, -C(=O)N(H)$R^{6a}$, -C(=O)N($R^{6a}$)$R^{6b}$,

-C(=O)O-$R^6$, -N($R^{6a}$)$R^{6b}$, -$NO_2$, -N(H)C(=O)$R^6$, -N($R^{6c}$)C(=O)$R^6$, -N(H)C(=O)N($R^{6a}$)$R^{6b}$, -N($R^{6c}$)C(=O)N($R^{6a}$)$R^{6b}$, -N(H)C(=O)O$R^6$, -N($R^{6c}$)C(=O)O$R^6$, -N(H)S(=O)$R^6$, -N($R^{6c}$)S(=O)$R^6$, -N(H)S(=O)$_2R^6$, -N($R^{6c}$)S(=O)$_2R^6$, -N=S(=O)($R^{6a}$)$R^{6b}$, -O$R^6$, -O(C=O)$R^6$, -O(C=O)N($R^{6a}$)$R^{6b}$, -O(C=O)O$R^6$, -S$R^6$, -S(=O)$R^6$, -S(=O)N(H)$R^6$, -S(=O)N($R^{6a}$)$R^{6b}$, -S(=O)$_2R^6$, -S(=O)$_2$N(H)$R^{6a}$, -S(=O)$_2$N($R^{6a}$)$R^{6b}$, -S(=O)(=N$R^{6c}$)$R^6$ group ;

$R^5$ represents a hydrogen atom, or a $C_1$-$C_6$-alkyl-, -$(CH_2)_n$-$C_2$-$C_6$-alkenyl, -$(CH_2)_n$-$C_2$-$C_6$-alkynyl, -$(CH_2)_m$-$C_3$-$C_6$-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-$C_1$-$C_6$-alkyl-, heteroaryl-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})$N-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, -$C_1$-$C_6$-alkyl-CN, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, $C_3$-$C_6$-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, $C_2$-$C_6$-alkenyl-, $C_4$-$C_8$-cycloalkenyl-, $C_2$-$C_6$-alkynyl-,aryl- or heteroaryl- group ;
wherein said $C_1$-$C_6$-alkyl-, -$(CH_2)_n$-$C_2$-$C_6$-alkenyl, -$(CH_2)_n$-$C_2$-$C_6$-alkynyl, -$(CH_2)_m$-$C_3$-$C_6$-cycloalkyl, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-$C_1$-$C_6$-alkyl-, heteroaryl-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})$N-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, -$C_1$-$C_6$-alkyl-CN, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, $C_3$-$C_6$-cycloalkyl-, 3- to 7-membered heterocycloalkyl-, $C_4$-$C_8$-cycloalkenyl-, aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 $R^8$ groups ;

$R^6$, $R^{6a}$, $R^{6b}$, $R^{6c}$
represent, independently from each other, a hydrogen atom, or a $C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, $C_3$-$C_6$-cycloalkyl-, $C_2$-$C_6$-alkenyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, aryl-$C_1$-$C_6$-alkyl- or heteroaryl-$C_1$-$C_6$-alkyl- group ;

$R^7$ represents a hydrogen or halogen atom, or a HO-, -CN, $C_1$-$C_6$-alkoxy-, $C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})N$-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, $C_2$-$C_6$-alkenyl, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$, $-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$ or $-S(=O)(=NR^{6c})R^6$ group ;

wherein said $C_1$-$C_6$-alkoxy-, aryl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2 or 3 $C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy-, halo-$C_1$-$C_6$-alkoxy-, $-C(=O)O-R^6$ or -OH groups;

or

when 2 $R^7$ groups are present ortho to each other on an aryl- or heteroaryl- ring, said 2 $R^7$ groups together form a bridge :

$*O(CH_2)_2O*$, $*O(CH_2)O*$, *NH(C(=O))NH*, wherein * represent the point of attachment to said aryl- or heteroaryl- ring ;

$R^8$ represents a hydrogen or halogen atom, or a -CN, $C_1$-$C_6$-alkoxy-, $C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkyl-, $R^{6a}(R^{6b})N$-$C_1$-$C_6$-alkyl-, HO-$C_1$-$C_6$-alkyl-, $C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, halo-$C_1$-$C_6$-alkoxy-$C_1$-$C_6$-alkyl-, $C_2$-$C_6$-alkenyl-, 3- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, $-C(=O)R^6$, $-C(=O)N(H)R^{6a}$, $-C(=O)N(R^{6a})R^{6b}$, $-C(=O)O-R^6$, $-N(R^{6a})R^{6b}$, $-NO_2$, $-N(H)C(=O)R^6$, $-N(R^{6c})C(=O)R^6$, $-N(H)C(=O)N(R^{6a})R^{6b}$, $-N(R^{6c})C(=O)N(R^{6a})R^{6b}$, $-N(H)C(=O)OR^6$, $-N(R^{6c})C(=O)OR^6$, $-N(H)S(=O)R^6$, $-N(R^{6c})S(=O)R^6$, $-N(H)S(=O)_2R^6$, $-N(R^{6c})S(=O)_2R^6$, $-N=S(=O)(R^{6a})R^{6b}$, $-OR^6$, $-O(C=O)R^6$, $-O(C=O)N(R^{6a})R^{6b}$, $-O(C=O)OR^6$, $-SR^6$, $-S(=O)R^6$, $-S(=O)N(H)R^6$, $-S(=O)N(R^{6a})R^{6b}$, $-S(=O)_2R^6$,

$-S(=O)_2N(H)R^6$, $-S(=O)_2N(R^{6a})R^{6b}$, $-S(=O)(=NR^{6c})R^6$ or $-S(=O)_2$-(3- to 7-membered heterocycloalkyl) group;

wherein said 3- to 7-membered heterocycloalkyl- or heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 $C_1$-$C_6$-alkyl- groups ;

m is an integer of 0, 1, 2, 3, 4, 5 or 6 ;

n is an integer of 0, 1, 2, 3, 4 or 5 ;

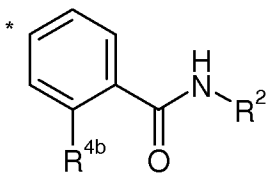
X represents $S(=O)_p$, O, $NR^6$, $CR^{6a}R^{6b}$ or $C=CR^{6a}R^{6b}$;

p is an integer of 0, 1 or 2 ;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

**3.** The combination according to claim 2, wherein

$R^A$ represents a



group;

wherein * indicates the point of attachment of said group with the rest of the molecule.

**4.** The combination according to claim 2 or 3, wherein

$R^2$ represents a methyl-, ethyl- or cyclopropyl- group ;

wherein said methyl- or ethyl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 groups selected from: halogen, -OH, -CN, $C_1$-$C_3$-alkoxy- ;

wherein said cyclopropyl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 groups selected from: halogen, -OH, -CN, $C_1$-$C_3$-alkyl-, $C_1$-$C_3$-alkoxy-, HO-$C_1$-$C_3$-alkyl-, halo-$C_1$-$C_3$-alkyl-.

**5.** The combination according to any one of claims 2 to 4, wherein

$R^3$ represents

a substituted or unsubstituted aryl-X- group, or

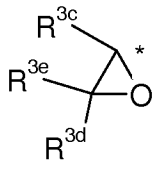
a substituted or unsubstituted heteroaryl-X- group.

**6.** The combination according to any one of claims 2 to 5, wherein

$R^3$ represents

$-C(R^{3a})(R^{3b})(R^{3c})$

or



;

wherein * indicates the point of attachment of said group with the rest of the molecule ;

wherein $R^{3a}$, $R^{3b}$ represent, independently from each other, a hydrogen atom or a halogen atom or a hydroxy-, $C_1$-$C_3$-alkyl-, HO-$C_1$-$C_3$-alkyl-, $C_2$-$C_4$-alkenyl-, halo-$C_1$-$C_3$-alkyl-, $C_1$-$C_3$-alkoxy- or halo-$C_1$-$C_3$-alkoxy- group, with the proviso that not both of $R^{3a}$ and $R^{3b}$ represent a hydrogen atom and not both of $R^{3a}$ and $R^{3b}$ represent a hydroxy group ;

or

$R^{3a}$, $R^{3b}$ together represent =O or $=C(R^{3d})(R^{3e})$ ;

or $R^{3a}$, $R^{3b}$ together with the carbon atom they are attached to, form a cyclopropyl- or cyclobutyl- ring ; wherein said cyclopropyl- or cyclobutyl- ring is optionally substituted, identically or differently, with 1 or 2 $R^{3d}$ groups ;

wherein $R^{3c}$ represents an aryl- or heteroaryl- group ; wherein said aryl- or heteroaryl- group is substituted, identically or differently, with 1, 2, 3 or 4 $R^7$ groups ;

and

wherein $R^{3d}$, $R^{3e}$ represent, independently from each other, a hydrogen atom or a $C_1$-$C_3$-alkyl- group.

**7.** The combination according to any one of claims 2 to 6, wherein

$R^5$ represents a $C_1$-$C_6$-alkyl-, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl- or heteroaryl- group ;
wherein said $C_1$-$C_6$-alkyl-, -$(CH_2)_m$-(3- to 7-membered heterocycloalkyl), aryl-, heteroaryl- group is optionally substituted, identically or differently, with 1, 2, 3 or 4 $R^8$ groups.

**8.** The combination according to claim 1, wherein compound A is selected from the group consisting of:

1-({6-[(2E/Z)-but-2-en-2-yl]-3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol,

1-({3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-6-[(1E/Z)-prop-1-en-1-yl]imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol,

3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-N-isobutyl-6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-8-amine,

3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-6-(pyridin-4-yl)-N-[(2S)-tetrahydrofuran-2-ylmethyl]imidazo[1,2-b]pyridazin-8-amine,

3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-6-(pyridin-4-yl)-N-[(2R)-tetrahydrofuran-2-ylmethyl]imidazo[1,2-b]pyridazin-8-amine,

3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-6-(4-fluorophenyl)-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine,

N-cyclopropyl-4-{6-(4-fluorophenyl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

1-({3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-6-(4-fluorophenyl)imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol,

1-({3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-8-yl}amino)-2-methylpropan-2-ol,

N-cyclopropyl-2-methyl-4-{6-(1-methyl-1H-pyrazol-5-yl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

3-(3-amino-1H-indazol-6-yl)-N-isobutyl-6-phenylimidazo[1,2-b]pyridazin-8-amine,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-phenylimidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-[8-(isobutylamino)-6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-3-yl]benzenecarbothioamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-phenylimidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(methylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-6-[(1E)-prop-1-en-1-yl]-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine,

N-cyclopropyl-4-{8-[(2-methoxy-2-methylpropyl)amino]-6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(methylsulfonyl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(4-fluorophenyl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[2-(hydroxymethyl)phenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-6-ethenyl-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine,

N-cyclopropyl-2-methyl-4-{6-[(1E)-prop-1-en-1-yl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(1E)-prop-1-en-1-yl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-[(2E)-but-2-en-2-yl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-6-(pyridin-4-yl)-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine,

6-[(2E)-but-2-en-2-yl]-3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine,

N-cyclopropyl-4-{6-(4-fluorophenyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-6-(pyridin-4-yl)-N-(tetrahydro-2H-pyran-2-ylmethyl)imidazo[1,2-b]pyridazin-8-amine,

(RS)-N-cyclopropyl-2-methyl-4-[8-{[(2-methyltetrahydrofuran-2-yl)methyl]amino}-6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-3-yl]benzamide,

N-cyclopropyl-2-methyl-4-[6-(pyridin-4-yl)-8-{[(2S)-tetrahydrofuran-2-ylmethyl]amino}imidazo[1,2-b]pyridazin-3-yl]benzamide,

N-cyclopropyl-4-{6-(4-fluorophenyl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzenecarbothioamide,

N-cyclopropyl-2-methyl-4-[6-(1-methyl-1H-pyrazol-5-yl)-8-{[(2R)-tetrahydrofuran-2-ylmethyl]amino}imidazo[1,2-b]pyridazin-3-yl]benzamide,

N-cyclopropyl-2-methyl-4-[6-(1-methyl-1H-pyrazol-5-yl)-8-{[(2S)-tetrahydrofuran-2-

ylmethyl]amino}imidazo[1,2-b]pyridazin-3-yl]benzamide,

N-cyclopropyl-2-methyl-4-[6-(pyridin-4-yl)-8-{[(2R)-tetrahydrofuran-2-ylmethyl]amino}imidazo[1,2-b]pyridazin-3-yl]benzamide,

N-cyclopropyl-4-{8-[(1,4-dioxan-2-ylmethyl)amino]-6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-(pyridin-4-yl)-8-[(tetrahydro-2H-pyran-2-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[2-(hydroxymethyl)phenyl]-8-[(2-methoxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-methoxy-2-methylpropyl)amino]-6-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-vinylimidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{8-[(3,3,3-trifluoropropyl)amino]-6-vinylimidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(cyclohex-1-en-1-yl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzenecarbothioamide,

N-cyclopropyl-4-{6-[2-(hydroxymethyl)phenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzenecarbothioamide,

N-cyclopropyl-4-{6-(1-methyl-1H-pyrazol-5-yl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzenecarbothioamide,

N-cyclopropyl-4-{6-[3-(hydroxymethyl)phenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzenecarbothioamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-3-yl}benzenecarbothioamide,

N-cyclopropyl-4-{6-cyclopropyl-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(4-fluorophenyl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-3-methoxybenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-3-yl}-3-methoxybenzamide,

N-cyclopropyl-3-hydroxy-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(phenylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(phenylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}-3-methoxybenzamide,

N-cyclopropyl-4-{6-(4-fluorophenyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-3-methoxybenzamide,

N-cyclopropyl-3-methoxy-4-{6-(1-methyl-1H-pyrazol-5-yl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[2-(hydroxymethyl)phenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-3-methoxybenzamide,

N-cyclopropyl-4-{6-[(2-methoxyphenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

(RS)-N-cyclopropyl-2-methyl-4-[8-{[(4-methylmorpholin-2-yl)methyl]amino}-6-(phenylsulfanyl)imidazo[1,2-b]pyridazin-3-yl]benzamide,

4-{8-[(2-amino-2-methylpropyl)amino]-6-(4-fluorophenyl)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{8-[(2-amino-2-methylpropyl)amino]-6-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{8-[(2-amino-2-methylpropyl)amino]-6-[2-(hydroxymethyl)phenyl]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(4-

hydroxyphenyl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(4-methoxyphenyl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(3-hydroxyphenyl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(3-methoxyphenyl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-3-hydroxybenzamide,

N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-3-methoxybenzamide

N-cyclopropyl-4-{6-[(4-hydroxy-3-methylphenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(5-fluoro-2-methylphenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-fluoro-3-methylphenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluoro-4-methylphenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluoro-5-methylphenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3,5-difluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-fluoro-2-methylphenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2-fluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-fluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-[(2E)-but-2-en-2-yl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-3-methoxybenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(2-hydroxyphenyl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(2-methoxyphenyl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-3-hydroxy-4-{6-(phenylsulfanyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-phenoxyimidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-phenoxy-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

4-{8-[(2-amino-2-methylpropyl)amino]-6-[(3-fluorophenyl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluoro-5-methylphenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(2-fluoro-5-methylphenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(3-cyanophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

(RS)-N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfinyl]-8-[(3,3,3-

trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfonyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-(phenylsulfanyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzenecarbothioamide,

4-{6-(3-chlorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(4-methoxyphenoxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluoro-5-methylphenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluoro-5-methylphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

4-{6-(4-chlorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{6-(3-chloro-4-fluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-(2,3-difluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(2-fluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(3-isopropylphenoxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(4-chloro-3-fluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-(3,5-dimethylphenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(3-methylphenoxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-chloro-8-[(2-sulfamoylethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide,

4-{6-chloro-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(2,3-dihydro-1,4-benzodioxin-6-yl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(naphthalen-1-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[3-(hydroxymethyl)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(4-fluorophenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(3-methylphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(2,3-dimethylphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

4-{6-[2-(acetylamino)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(quinolin-3-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

4-{3-[4-(cyclopropylcarbamoyl)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-6-yl}-N,N-dimethylbenzamide,

N-cyclopropyl-4-{6-(2-methylphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(quinolin-5-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(quinolin-4-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

4-{6-(4-carbamoylphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide,

4-{6-(3-carbamoylphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide,

N-cyclopropyl-4-{6-(isoquinolin-4-yl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

4,4'-{8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazine-3,6-diyl}bis(N-cyclopropylbenzamide),

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(isoquinolin-5-yl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

3-{3-[4-(cyclopropylcarbamoyl)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-6-yl}-N-methylbenzamide,

4-{3-[4-(cyclopropylcarbamoyl)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-6-yl}-N-(propan-2-yl)benzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(thiophen-2-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(thiophen-3-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-[4-

(trifluoromethyl)phenyl]imidazo[1,2-b]pyridazin-3-yl}benzamide,

4-[6-(3-chlorophenyl)-8-(isobutylamino)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropylbenzamide,

N-cyclopropyl-4-{6-(3-methoxyphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

4-{6-[3-(acetylamino)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide,

4-{6-(1-benzofuran-2-yl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide,

N-cyclopropyl-4-{6-(3-fluorophenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(2-methoxyphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

4-{6-(biphenyl-4-yl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide,

N-cyclopropyl-4-{6-(2,3-dichlorophenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(2-fluorophenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[4-(hydroxymethyl)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

3-{3-[4-(cyclopropylcarbamoyl)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-6-yl}-N-(propan-2-yl)benzamide,

N-cyclopropyl-3-{3-[4-(cyclopropylcarbamoyl)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-6-yl}benzamide,

4-{6-(1,3-benzodioxol-5-yl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(pyridin-3-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(2-hydroxyphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(3-hydroxyphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(4-hydroxyphenyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-[4-(methylsulfonyl)phenyl]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(pyrimidin-5-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(quinolin-6-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(imidazo[1,2-a]pyridin-6-yl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-(6-{4-[(methylcarbamoyl)amino]phenyl}-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl)benzamide,

4-{6-(5-cyanopyridin-3-yl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide,

N-cyclopropyl-4-{6-[4-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

5-{3-[4-(cyclopropylcarbamoyl)phenyl]-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-6-yl}-N-methylpyridine-2-carboxamide,

N-cyclopropyl-4-(6-{4-[(dimethylcarbamoyl)amino]phenyl}-8-[(2-

methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl)benzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-phenylimidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[3-(hydroxymethyl)phenyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[4-(hydroxymethyl)phenyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-3-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(furan-3-yl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(6-ethoxypyridin-3-yl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3,5-dimethyl-1,2-oxazol-4-yl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(1H-pyrazol-3-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(1-methyl-1H-pyrrol-2-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyrimidin-5-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(2-methylpyridin-4-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[4-fluoro-3-(hydroxymethyl)phenyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3,6-dihydro-2H-pyran-4-yl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(quinolin-5-yloxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(quinolin-6-yloxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-(quinolin-6-yloxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-2-methyl-4-{6-(quinolin-5-yloxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

4-{6-(cyclohexylsulfanyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{6-(cyclohexylsulfanyl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-3-yloxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-(pyridin-3-yloxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-6-ethenyl-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine,

4-{6-chloro-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

4-{6-chloro-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide,

4-{6-chloro-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-methylbenzamide,

4-{6-chloro-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-(propan-2-yl)benzamide,

2-chloro-4-{6-chloro-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-methylbenzamide,

2-chloro-4-{6-chloro-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide,

4-{6-chloro-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-fluoro-N-(propan-2-yl)benzamide,

6-chloro-3-[3-(cyclopropylamino)-1,2-benzoxazol-6-yl]-N-(2-methylpropyl)imidazo[1,2-b]pyridazin-8-amine,

6-chloro-3-[4-(2-cyclopropyl-1H-imidazol-5-yl)phenyl]-N-(2-methylpropyl)imidazo[1,2-b]pyridazin-8-amine,

4-{6-chloro-8-[(thiophen-2-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,N-dimethylbenzamide,

2-chloro-4-{6-chloro-8-[(thiophen-2-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-methylbenzamide,

2-chloro-4-{6-chloro-8-[(thiophen-2-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropylbenzamide,

4-{6-chloro-8-[(thiophen-2-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-fluoro-N-(propan-2-yl)benzamide,

6-chloro-3-[3-(cyclopropylamino)-1,2-benzoxazol-6-yl]-N-(thiophen-2-ylmethyl)imidazo[1,2-b]pyridazin-8-amine,

4-{6-chloro-8-[(thiophen-2-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-methylbenzamide,

4-{6-chloro-8-[(thiophen-2-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-[8-({(2S)-2-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-hydroxyethyl}amino)-6-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-3-yl]benzamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(methylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

(RS)-N-cyclopropyl-2-methyl-4-{8-[(2-methylpropyl)amino]-6-[(tetrahydrofuran-2-ylmethyl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-2-methyl-4-{8-[(2-methylpropyl)amino]-6-(1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-2-methyl-4-{8-[(2-methylpropyl)amino]-6-(methylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-2-methyl-4-{8-[(2-methylpropyl)amino]-6-(phenylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-2-methyl-4-{8-[(2-methylpropyl)amino]-6-(phenylsulfonyl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-N-(2-hydroxyethyl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazine-6-carboxamide,

N-cyclopropyl-4-{8-[(2-methylpropyl)amino]-6-(methylsulfonyl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-2-methyl-4-{8-[(2-methylpropyl)amino]-6-(propylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-2-methyl-4-{8-[(2-methylpropyl)amino]-6-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-2-methyl-4-{6-(methylsulfanyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[(2-hydroxyethyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-chloro-8-[(3,3,3-trifluoro-2-hydroxypropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-(methylsulfanyl)-8-[(3,3,3-trifluoro-2-hydroxypropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-2-methyl-4-{6-(phenylsulfanyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-2-methyl-4-{6-(1-methyl-1H-pyrazol-5-yl)-8-[(3,3,3-trifluoro-2-hydroxypropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-(6-{[2-(diethylamino)ethyl]sulfanyl}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-{8-[(3-hydroxypropyl)amino]-6-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-(phenylsulfonyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

4-{6-(5-cyanopyridin-3-yl)-8-[(2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(phenylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-(6-{[2-(morpholin-4-yl)ethyl]sulfanyl}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl)benzamide,

N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfanyl]-8-[(3,3,3-trifluoro-2-hydroxypropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3,3-dimethylbutyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2,6-difluorophenyl)sulfanyl]-8-[(2-hydroxy-2-

methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-3-hydroxybenzamide,

N-cyclopropyl-4-{6-[2-(hydroxymethyl)phenyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-[(2E)-but-2-en-2-yl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[2-(fluoromethyl)phenyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(2-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2-hydroxyphenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3,3-dimethylbutyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-methoxyphenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-(pyridin-4-yl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

(RS)-N-cyclopropyl-4-[6-(4-fluorophenyl)-8-{[(4-methylmorpholin-2-yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-4-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-[6-(methylsulfanyl)-8-{[2-(morpholin-4-ylsulfonyl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]benzamide,

N-cyclopropyl-4-{6-(4-fluoro-2-methylphenyl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(2-fluorophenyl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(5-cyanopyridin-3-yl)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

(RS)-4-{6-(cyclohex-1-en-1-yl)-8-[(3,3,3-trifluoro-2-hydroxypropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-[8-{[(1-methyl-1H-pyrazol-5-yl)methyl]amino}-6-(methylsulfanyl)imidazo[1,2-b]pyridazin-3-yl]benzamide,

N-cyclopropyl-4-{6-[(3-hydroxyphenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-(8-[(2-hydroxy-2-methylpropyl)amino]-6-{[2-(morpholin-4-yl)ethyl]sulfanyl}imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

(RS)-N-cyclopropyl-4-{6-[(2,2-difluorocyclopropyl)methoxy]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-(8-[(2-hydroxy-2-methylpropyl)amino]-6-{[(1E)-2,3,3-trifluoro-4-hydroxybut-1-en-1-yl]oxy}imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(2,2,3,3-tetrafluoro-4-hydroxybutoxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-(8-[(2-hydroxy-2-methylpropyl)amino]-6-{[4-(trifluoromethyl)phenyl]sulfanyl}imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-phenoxyimidazo[1,2-b]pyridazin-3-yl}benzenecarbothioamide,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)

amino]imidazo[1,2-b]pyridazin-3-yl}benzenecarbothioamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(phenylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}benzenecarbothioamide,

N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzenecarbothioamide,

N-cyclopropyl-2-methyl-4-(6-{[4-(trifluoromethyl)phenyl]sulfanyl}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl)benzamide,

N-cyclopropyl-4-{6-[(2,5-difluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3,4-difluorophenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-fluorophenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3,5-difluorophenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2,3-difluorophenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(4-fluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3,4-difluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2,5-difluorophenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(4-isopropoxyphenoxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(4-isopropoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(2,3-difluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(2-fluoro-5-methylphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3,4-difluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(2-thienylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3,5-difluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-(8-[(2-hydroxy-2-methylpropyl)amino]-6-{[(3S)-2-oxopyrrolidin-3-yl]oxy}imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(6-methylpyridin-3-yl)oxy]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyrimidin-5-yloxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(3-chlorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{6-(4-chlorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2-fluorophenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(5-fluoro-2-methylphenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-(6-{[2-(hydroxymethyl)phenyl]sulfanyl}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(3-methoxy-

phenyl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

(RS)-N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyrrolidin-3-ylamino)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(3-isopropyl-phenyl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-2-yloxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[3-(2-hydroxy-2-methylpropoxy)phenoxy]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfanyl]-8-[(2-hydroxy-ethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(2-hydroxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-(6-{[(1E)-2,3,3-trifluoro-4-hydroxybut-1-en-1-yl]oxy}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl)benzamide,

N-cyclopropyl-2-methyl-4-{6-(2,2,3,3-tetrafluoro-4-hydroxybutoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

2-{3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-6-yl}-5-fluoro-benzoic acid methyl ester,

N-cyclopropyl-4-{6-(2-hydroxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluoro-5-methylphenoxy)-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(2-fluorophenoxy)-8-[(tetrahydro-2H-thiopyran-4-

ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-(phenylsulfanyl)-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[(3-fluorophenyl)sulfanyl]-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluoro-5-methylphenyl)sulfanyl]-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-hydroxyphenyl)sulfanyl]-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-(pyridin-3-yloxy)-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[(2-hydroxyphenyl)sulfanyl]-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(4-fluorophenoxy)-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

4-{6-(4-chloro-3-fluorophenoxy)-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{6-(4-chlorophenoxy)-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-(2,3-difluorophenoxy)-8-[(tetrahydro-2H-thiopyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-[6-(4-chlorophenoxy)-8-({[(cis/trans)-1-oxidotetrahydro-2H-thiopyran-4-yl]methyl}amino)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide,

4-[6-(4-chlorophenoxy)-8-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-[6-(4-fluorophenoxy)-8-({[(cis/trans)-1-oxidotetrahydro-2H-thiopyran-4-yl]methyl}amino)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[8-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}-6-(4-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-[8-({[(cis)-1-oxidotetrahydro-2H-thiopyran-4-yl]methyl}amino)-6-(pyridin-3-yloxy)imidazo[1,2-b]pyridazin-3-yl]benzamide,

N-cyclopropyl-2-methyl-4-[8-({[(trans)-1-oxidotetrahydro-2H-thiopyran-4-yl]methyl}amino)-6-(pyridin-3-yloxy)imidazo[1,2-b]pyridazin-3-yl]benzamide,

N-cyclopropyl-4-[8-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}-6-(pyridin-3-yloxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[8-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}-6-(2-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-({[(cis/trans)-1-oxidotetrahydro-2H-thiopyran-4-yl]methyl}amino)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[8-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-{6-[4-fluoro-2-(hydroxymethyl)phenyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3,4-difluorophenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-(8-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}-6-[(3-fluorophenyl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-[8-{[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl]amino}-6-(phenylsulfanyl)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-[8-({[(cis)-1-oxidotetrahydro-2H-thiopyran-4-yl]methyl}amino)-6-(phenylsulfanyl)imidazo[1,2-b]pyridazin-3-yl]benzamide,

N-cyclopropyl-2-methyl-4-[8-({[(trans)-1-oxidotetrahydro-2H-thiopyran-4-yl]methyl}amino)-6-(phenylsulfanyl)imidazo[1,2-b]pyridazin-3-yl]benzamide,

N-cyclopropyl-4-(6-[(3-fluorophenyl)sulfanyl]-8-({[(cis)-1-oxidotetrahydro-2H-

thiopyran-4-yl]methyl}amino)imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-(6-[(3-fluorophenyl)sulfanyl]-8-({[(trans)-1-oxidotetrahydro-2H-thiopyran-4-yl]methyl}amino)imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-fluorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-anilino-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3,4-difluorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(3-methylphenyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(5-fluoro-2-methylphenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-[(4-chlorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[(1-methylpiperidin-4-yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[8-{[3-(dimethylamino)propyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[2-(methylsulfonyl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

4-{8-[(2-amino-2-methylpropyl)amino]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{8-[(azetidin-3-ylmethyl)amino]-6-phenoxyimidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(4H-1,2,4-triazol-3-ylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(4-methyl-1H-imidazol-2-yl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(1H-imidazol-2-ylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(1-methyl-1H-pyrazol-5-yl)oxy]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[4-(piperazin-1-yl)phenoxy]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(1-methyl-1H-pyrazol-4-yl)oxy]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

tert-butyl 4-[4-({3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]piperazine-1-carboxylate,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(3-hydroxy-3-methylbutyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(benzyloxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-[8-{[(1,1-dioxidotetrahydrothiophen-3-yl)methyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(tetrahydrofuran-3-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[(1-methyl-5-oxopyrrolidin-3-yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[8-{[(3,3-difluorocyclobutyl)methyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-4-yloxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-4-ylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-2-ylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(tetrahydro-2H-pyran-4-ylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(cyclopentylsulfanyl)-8-[(2-hydroxy-2-methylpropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(piperidin-1-yl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{8-[(azetidin-3-ylmethyl)amino]-6-[2-(hydroxymethyl)phenyl] imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

tert-butyl 3-[({3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-6-[2-(hydroxymethyl)phenyl]imidazo[1,2-b]pyridazin-8-yl}amino)methyl]azetidine-1-carboxylate,

N-cyclopropyl-4-(8-{[(4-hydroxy-4-methylcyclohexyl)methyl]amino}-6-[2-(hydroxymethyl)phenyl]imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-{8-[(3-hydroxy-3-methylbutyl)amino]-6-[2-(hydroxymethyl)phenyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

(RS)-N-cyclopropyl-4-{6-[2-(hydroxymethyl)phenyl]-8-[(4-hydroxypentyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

(RS)-N-cyclopropyl-4-{8-[(4-hydroxy-3-methylbutyl)amino]-6-[2-(hydroxymethyl)phenyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-(6-[2-(hydroxymethyl)phenyl]-8-{[(1-methyl-5-oxopyrrolidin-3-yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

(RS)-N-cyclopropyl-4-{6-[2-(hydroxymethyl)phenyl]-8-[(tetrahydrofuran-3-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[2-(hydroxymethyl)phenyl]-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{8-[(2-cyanoethyl)amino]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{6-[(4-chloro-2-fluorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(5-methoxy-2-methylphenyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[4-fluoro-2-(hydroxymethyl)phenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3,5-difluorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2,3-difluorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluoro-4-methoxyphenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(4-methoxyphenyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-[(3-chlorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2,4-difluorophenyl)amino]-8-[(2-hydroxy-2-

methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-2-ylamino)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-fluorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-3-ylamino)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2-fluoro-4-methylphenyl)sulfanyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(3-isopropoxyphenoxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2-fluoro-4-methylphenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

4-{6-[4-chloro-2-(hydroxymethyl)phenyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{6-[4-chloro-2-(hydroxymethyl)phenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyridin-4-ylamino)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(6-methoxypyridin-3-yl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2-fluoro-5-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-anilino-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2-fluorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-(6-{[2-(hydroxymethyl)phenyl]amino}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluoro-5-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-[(4-chloro-3-fluorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3,4-difluorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-[(4-chlorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(5-fluoro-2-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-[(4-chloro-2-fluorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{6-[(5-chloro-2-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3,5-difluorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-[(3-chlorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2,3-difluorophenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-[3-(propan-2-yloxy)phenoxy]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[(4-fluoro-3-methylphenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2-fluoro-5-methylphenyl)amino]-8-[(2-hydroxy-2-

methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2-fluorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(3-isopropylphenyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-(6-{[4-(2-hydroxyethyl)phenyl]amino}-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluoro-2-methylphenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2-methoxyphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-[2-(methylamino)phenoxy]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(5-fluoro-2-methylphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(5-fluoro-2-methylphenoxy)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-(6-{[4-chloro-2-(hydroxymethyl)phenyl]sulfanyl}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide,

4-(6-{[4-chloro-2-(hydroxymethyl)phenyl]sulfanyl}-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluoro-5-methylphenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(2-aminophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{6-(2-amino-4-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino] imidazo[1,2-

b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-fluoro-2-hydroxyphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(2-chloro-3-fluorophenoxy)-8-[(2-hydroxy-2-methylpropyl)amino] imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(3-methoxy-2-methylphenyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2-hydroxyphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-fluoro-3-methoxyphenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-[(4-chloro-3-fluorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(2-methoxyphenyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(3-methoxyphenyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-[(5-chloro-2-methylphenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{6-[(2-chloro-4-fluorophenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(6-fluoropyridin-3-yl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(cyclopentylamino)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{6-(cyclopent-3-en-1-ylamino)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-ethenylphenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(6-fluoropyridin-3-yl)oxy]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

5-({3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)nicotinamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(pyrazin-2-ylsulfanyl)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(4-methyl-4H-1,2,4-triazol-3-yl)sulfanyl]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-(1H-pyrazol-5-yloxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(5-methyl-1H-pyrazol-3-yl)oxy]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(cyclohexylamino)-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{6-[(2-amino-4-fluorophenyl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[2-methoxy-3-(propan-2-yl)phenoxy]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-[(4-methyl-4H-1,2,4-triazol-3-yl)sulfanyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-2-methyl-4-{6-(pyrazin-2-ylsulfanyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-(6-{[(1RS,2RS)-2-hydroxycyclohexyl]oxy}-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-fluoro-3-methoxyphenyl)amino]-8-[(3,3,3-

trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-[(3-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[(3-fluoro-4-methoxyphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-methoxyphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-methoxy-2-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-(6-{[4-(2-hydroxyethyl)phenyl]amino}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-fluoro-3-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(6-methoxypyridin-3-yl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(5-methoxy-2-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(2-hydroxyphenyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-fluoro-2-methoxyphenyl)amino]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-(6-{[3-(propan-2-yl)phenyl]amino}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl)benzamide,

N-cyclopropyl-4-(6-{[2-(hydroxymethyl)phenyl]amino}-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

4-(6-{[4-(2-aminoethyl)phenyl]amino}-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(6-fluoropyridin-3-yl)oxy]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-2-methyl-4-{6-(pyridin-3-ylamino)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[(6-fluoropyridin-3-yl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[2-hydroxy-3-(propan-2-yl)phenoxy]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-fluoro-3-hydroxyphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(5-hydroxy-2-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2-hydroxy-2-methylpropyl)amino]-6-[(3-hydroxyphenyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3,4-difluorophenyl)amino]-8-[(4,4,4-trifluorobutyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(5-fluoro-2-methylphenyl)amino]-8-[(4,4,4-trifluorobutyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-fluoro-5-methylphenyl)sulfanyl]-8-[(4,4,4-

trifluorobutyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2,3-difluorophenyl)amino]-8-[(4,4,4-trifluorobutyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-[(5-chloro-2-methylphenyl)amino]-8-[(4,4,4-trifluorobutyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluoro-5-methylphenoxy)-8-[(4,4,4-trifluorobutyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(cyclopentylamino)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-hydroxy-2-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(cyclopentyloxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(5-hydroxy-2-methylphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(4-fluoro-2-methoxyphenyl)amino]-8-[(4,4,4-trifluorobutyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[2-fluoro-3-(methylsulfanyl)phenoxy]-8-[(2-hydroxy-2-methylpropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methyl-N-(1-methylcyclopropyl)benzamide,

4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-(1-methoxycyclopropyl)-2-methylbenzamide,

N-(1-cyanocyclopropyl)-4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

3-(3-amino-1H-indazol-6-yl)-6-(3-fluorophenoxy)-N-(3,3,3-trifluoropropyl)imidazo[1,2-b]pyridazin-8-amine,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[(5-fluoropyridin-3-yl)oxy]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(2-amino-5-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-(1,2,3,4-tetrahydroquinolin-8-yloxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(8-hydroxy-3,4-dihydroquinolin-1(2H)-yl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-[(2-oxo-1,2-dihydroquinolin-8-yl)oxy]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-2-methyl-4-{6-[(2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)oxy]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-2-methyl-4-{6-(3-methylphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(4-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(2-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-(2-methylphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(3-fluoro-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-(6-{[4-(acetylamino)pyridin-3-yl]oxy}-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-

b]pyridazin-3-yl)-N-cyclopropyl-2-methylbenzamide,

4-{6-(2-amino-3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-[(2-fluoro-6-hydroxyphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-(4-methylphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[(4-fluoro-2-hydroxyphenyl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(3-hydroxypyridin-4-yl)amino]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{6-(1-phenylethenyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-(3-fluoro-4-methoxybenzyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluoro-4-methylbenzyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(3-bromobenzyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoro-2-hydroxypropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-[8-{[2-(dimethylamino)ethyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[(1-methyl-1H-pyrazol-3-yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(1H-pyrazol-3-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-({[3-(hydroxymethyl)oxetan-3-yl]methyl}amino)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2,3-dihydroxypropyl)amino]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-[8-{[3-(dimethylamino)-3-oxopropyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[8-{[(4,4-difluorocyclohexyl)methyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(oxetan-3-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(1H-tetrazol-5-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-[8-{[2-(dimethylamino)-2-methylpropyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[2-methyl-2-(morpholin-4-yl)propyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[2-(piperidin-1-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[2-(4-methylpiperazin-1-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[2-(pyrrolidin-1-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-({3-

[methyl(methylcarbamoyl)amino]propyl}amino)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

4-[8-{[2-(acetylamino)ethyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[3-(piperidin-1-yl)propyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[3-(morpholin-4-yl)propyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[3-(pyrrolidin-1-yl)propyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[3-(methylsulfonyl)propyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

4-[8-{[3-(acetylamino)propyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-(methylamino)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[2-(1H-tetrazol-5-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-{8-[(2,2-difluoroethyl)amino]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-[8-{[4-(dimethylamino)butyl]amino}-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-fluorophenoxy)-8-[(2,2,2-trifluoroethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[2-(1H-pyrazol-1-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(2,3-difluorophenoxy)-8-{[2-

(methylsulfonyl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(5-fluoro-2-methylphenoxy)-8-{[2-(methylsulfonyl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluoro-4-methoxyphenoxy)-8-{[2-(methylsulfonyl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(2-fluoro-4-methoxyphenoxy)-8-{[2-(methylsulfonyl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

4-{8-[(2-amino-2-methylpropyl)amino]-6-(3,4-difluorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{8-[(2-amino-2-methylpropyl)amino]-6-(4-chlorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide

4-{8-[(2-amino-2-methylpropyl)amino]-6-(pyridin-3-yloxy)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-[6-(4-chlorophenoxy)-8-{[2-(dimethylamino)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-[8-{[2-(dimethylamino)ethyl]amino}-6-(pyridin-3-yloxy)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3,4-difluorophenoxy)-8-{[2-(dimethylamino)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(2,3-difluorophenoxy)-8-{[(1-methylpiperidin-4-yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-[8-{[(1-methylpiperidin-4-yl)methyl]amino}-6-(pyridin-3-yloxy)imidazo[1,2-b]pyridazin-3-yl]benzamide,

N-cyclopropyl-4-[6-(2,3-difluorophenoxy)-8-(methylamino)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3,4-difluorophenoxy)-8-(methylamino)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(5-fluoro-2-methylphenoxy)-8-(methylamino)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-{8-(methylamino)-6-[2-(methylamino)phenoxy]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-cyclopropyl-4-{6-[(2-hydroxyphenyl)(methyl)amino]-8-(methylamino)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[(5-fluoropyridin-3-yl)oxy]-8-(methylamino)imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-[6-(2-fluoro-4-methoxyphenoxy)-8-(methylamino)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluoro-4-methoxyphenoxy)-8-(methylamino)imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(2,3-difluorophenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-[6-(5-fluoro-2-methylphenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-2-methyl-4-(6-[2-(methylamino)phenoxy]-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl)benzamide,

N-cyclopropyl-4-(6-[(2-hydroxyphenyl)(methyl)amino]-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-[6-(3,4-difluorophenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-cyclopropyl-4-(6-[(5-fluoropyridin-3-yl)oxy]-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl)-2-methylbenzamide,

N-cyclopropyl-4-[6-(3-fluorophenoxy)-8-{[(1-methylazetidin-3-yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

4-{8-[(azetidin-3-ylmethyl)amino]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-

N-cyclopropyl-2-methylbenzamide,

N-cyclopropyl-4-[6-(2,3-difluorophenoxy)-8-{[(1-methylazetidin-3-yl)methyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

4-{8-[(azetidin-3-ylmethyl)amino]-6-(2,3-difluorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{8-[(azetidin-3-ylmethyl)amino]-6-[(5-fluoropyridin-3-yl)oxy]imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{8-[(azetidin-3-ylmethyl)amino]-6-(5-fluoro-2-methylphenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

4-{8-[(3-aminopropyl)amino]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-cyclopropyl-2-methylbenzamide,

3-({3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-8-yl}amino)propane-1-sulfonic acid,

2-({3-[4-(cyclopropylcarbamoyl)-3-methylphenyl]-6-(3-fluorophenoxy)imidazo[1,2-b]pyridazin-8-yl}amino)ethanesulfonic acid,

N-(1-cyanocyclopropyl)-4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

N-ethyl-4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-isopropyl-2-methylbenzamide,

4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methyl-N-(3,3,3-trifluoropropyl)benzamide,

4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methyl-N-(2,2,3,3,3-pentafluoropropyl)benzamide,

N-(2,2-difluoroethyl)-4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-isobutyl-2-methylbenzamide,

4-{6-(4-chlorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(4-chlorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-ethyl-2-methylbenzamide,

4-{6-(2-fluoro-4-hydroxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

N-ethyl-4-{6-(2-fluoro-4-hydroxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-[6-(3,4-difluorophenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-N,2-dimethylbenzamide,

N,2-dimethyl-4-[6-(2-methylphenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]benzamide,

4-[6-(4-methoxyphenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-N,2-dimethylbenzamide,

4-[6-(2-fluoro-4-methoxyphenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-N,2-dimethylbenzamide,

4-[6-(5-fluoro-2-methylphenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-N,2-dimethylbenzamide,

4-{6-(3,4-difluorophenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

N,2-dimethyl-4-{6-(2-methylphenoxy)-8-[(tetrahydro-2H-pyran-4-

ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

4-{6-(3-fluorophenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(4-methoxyphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(5-fluoro-2-methylphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(3-fluoro-4-methoxyphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(3,4-difluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(3-fluorophenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(5-fluoro-2-methylphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(3-fluoro-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{8-[(2,2-difluoroethyl)amino]-6-(3,4-difluorophenoxy)imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{8-[(2,2-difluoroethyl)amino]-6-(2-fluoro-4-methoxyphenoxy)imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(2,3-difluorophenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(3,4-difluorophenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{8-[(2-methoxyethyl)amino]-6-(2-methylphenoxy)imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(5-fluoro-2-methylphenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{6-(3-fluoro-4-methoxyphenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-{8-[(2-methoxyethyl)amino]-6-phenoxyimidazo[1,2-b]pyridazin-3-yl}-N,2-dimethylbenzamide,

4-[6-(3,4-difluorophenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-N-ethyl-2-methylbenzamide,

N-ethyl-2-methyl-4-[6-(2-methylphenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]benzamide,

N-ethyl-4-[6-(4-methoxyphenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-ethyl-4-[6-(2-fluoro-4-methoxyphenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-ethyl-4-[6-(5-fluoro-2-methylphenoxy)-8-{[2-(morpholin-4-yl)ethyl]amino}imidazo[1,2-b]pyridazin-3-yl]-2-methylbenzamide,

N-ethyl-2-methyl-4-(8-{[2-(morpholin-4-yl)ethyl]amino}-6-phenoxyimidazo[1,2-b]pyridazin-3-yl)benzamide,

4-{6-(3,4-difluorophenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-ethyl-2-methylbenzamide,

N-ethyl-2-methyl-4-{6-(2-methylphenoxy)-8-[(tetrahydro-2H-pyran-4-

ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-ethyl-4-{6-(4-methoxyphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-ethyl-4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-ethyl-4-{6-(5-fluoro-2-methylphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-ethyl-4-{6-(3-fluoro-4-methoxyphenoxy)-8-[(tetrahydro-2H-pyran-4-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-ethyl-2-methyl-4-{6-(2-methylphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}benzamide,

N-ethyl-4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-ethyl-4-{6-(5-fluoro-2-methylphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-ethyl-4-{6-(3-fluoro-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

4-{8-[(2,2-difluoroethyl)amino]-6-(2-fluoro-4-methoxyphenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-ethyl-2-methylbenzamide,

4-{8-[(2,2-difluoroethyl)amino]-6-(5-fluoro-2-methylphenoxy)imidazo[1,2-b]pyridazin-3-yl}-N-ethyl-2-methylbenzamide,

4-{6-(3,4-difluorophenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-N-ethyl-2-methylbenzamide,

N-ethyl-4-{6-(2-fluoro-4-methoxyphenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-ethyl-4-{6-(5-fluoro-2-methylphenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-ethyl-4-{6-(3-fluoro-4-methoxyphenoxy)-8-[(2-methoxyethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[1-(3-fluoro-4-methoxyphenyl)ethenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[difluoro(3-fluoro-4-methoxyphenyl)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

(RS)-N-cyclopropyl-4-{6-[(3-fluoro-2-hydroxyphenyl)(hydroxy)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

(R)-N-cyclopropyl-4-{6-[(3-fluoro-2-hydroxyphenyl)(hydroxy)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

(S)-N-cyclopropyl-4-{6-[(3-fluoro-2-hydroxyphenyl)(hydroxy)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

(RS)-N-cyclopropyl-4-{6-[1-(3-fluoro-2-hydroxyphenyl)-1-hydroxyethyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

(R)-N-cyclopropyl-4-{6-[1-(3-fluoro-2-hydroxyphenyl)-1-hydroxyethyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

(S)-N-cyclopropyl-4-{6-[1-(3-fluoro-2-hydroxyphenyl)-1-hydroxyethyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

(RS)-N-cyclopropyl-4-{6-[fluoro(3-fluorophenyl)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

(R)-N-cyclopropyl-4-{6-[fluoro(3-fluorophenyl)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

(S)-N-cyclopropyl-4-{6-[fluoro(3-fluorophenyl)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[difluoro(3-fluorophenyl)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(3-methoxybenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-[1-(3-methoxyphenyl)vinyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

N-cyclopropyl-4-{6-(4-methoxybenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide, and

N-cyclopropyl-4-{6-[1-(4-methoxyphenyl)vinyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

*N*-cyclopropyl-4-{6-[(2,5-difluorophenyl)(hydroxy)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide,

*N*-cyclopropyl-4-{6-(2,5-difluorobenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide,

*N*-cyclopropyl-4-{6-(3-fluoro-4-methoxybenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide,

*N*-cyclopropyl-4-{6-(2,3-difluorobenzoyl)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide,

*N*-cyclopropyl-4-{6-[1-(2,3-difluorophenyl)vinyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide,

*N*-cyclopropyl-4-{6-[difluoro(4-methoxyphenyl)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide,

*N*-cyclopropyl-4-{6-[1-(2,3-difluorophenyl)cyclopropyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide,

*N*-cyclopropyl-4-{6-[(2,3-difluorophenyl)(difluoro)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide,

*N*-cyclopropyl-4-{6-[1-(2,5-difluorophenyl)vinyl]-8-[(3,3,3-

trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide,

*N*-cyclopropyl-4-{6-[1-(2,5-difluorophenyl)cyclopropyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide,

*N*-cyclopropyl-4-{6-[(2,5-difluorophenyl)(difluoro)methyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide,

*N*-cyclopropyl-4-{6-[1-(5-fluoro-2-hydroxyphenyl)ethenyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide,

*N*-cyclopropyl-4-{6-[1-(5-fluoro-2-hydroxyphenyl)cyclopropyl]-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide,

*N*-cyclopropyl-4-{6-(2,3-difluoro-4-methoxyphenoxy)-8-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide,

*N*-cyclopropyl-4-{6-(2,3-difluoro-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-*b*]pyridazin-3-yl}-2-methylbenzamide,

*N*-cyclopropyl-4-{6-(3-fluoro-4-methoxyphenoxy)-8-[(oxetan-3-ylmethyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide,

or a salt, particularly a pharmaceutically acceptable salt, a tautomer, or a stereoisomer of said compound, or a salt, particularly a pharmaceutically acceptable salt, of said tautomer or said stereoisomer.

**9.** The combination according to any one of claims 1 to 8, wherein compound B is selected from the group consisting of:
Obatoclax, Navitoclax, beclanorsen, VMD-8018, oblimersen, apogossypol, 1133719, PNT-100, HG-1113, S-44563, ABT-731, ONT-701, BP-100-1.02, AT-101.

**10.** Use of a combination according to any one of claims 1 to 9 for the preparation of a medicament for the treatment or prophylaxis of a cancer, particularly hepatocyte carcinoma, lung cancer, in particular non-small cell

lung carcinoma, colorectal cancer, melanoma, pancreatic cancer or breast cancer.

**11.** A method of treatment or prophylaxis of a cancer, particularly hepatocyte carcinoma, lung cancer, in particular non-small cell lung carcinoma, colorectal cancer, melanoma, pancreatic cancer or breast cancer, in a subject, comprising administering to said subject a therapeutically effective amount of a combination accoring to any one of claims 1 to 9.

**12.** A kit comprising a combination of :
one or more compounds A as defined in any one of the claims 1 to 8;
one or more compounds B as defined in any of claims 1 or 9;
and, optionally, one or more further pharmaceutical agents C;
in which optionally both or either of said components A and B are in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially.

**13.** Use of an anti-apoptotic protein from the Bcl-2 family as a sensitizer of cells to Mps-1 inhibitors.

**14.** Use of the ratio of pro-apoptotic and anti-apoptotic proteins from the Bcl-2 family in a biological sample as a biomarker for a Mps-1 kinase inhibitor treatment.

## Figures

A


Fig. 1A

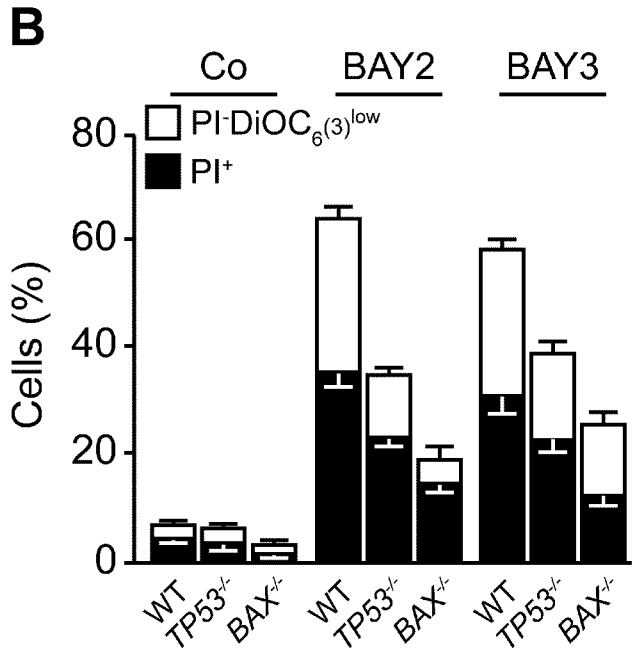

B
Co
BAY2
BAY3
PI-DiOC6(3)low
PI+
Cells (%)
80
60
40
20
0
WT
TP53-/-
BAX-/-
WT
TP53-/-
BAX-/-
WT
TP53-/-
BAX-/-

Fig. 1B

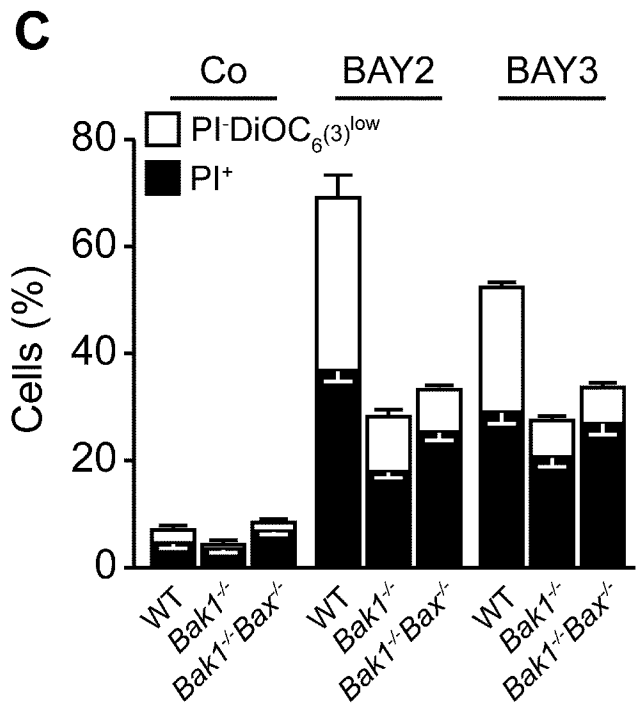

C
Co
BAY2
BAY3
PI-DiOC6(3)low
PI+
Cells (%)
80
60
40
20
0
WT
Bak1-/-
Bak1-/-Bax-/-
WT
Bak1-/-
Bak1-/-Bax-/-
WT
Bak1-/-
Bak1-/-Bax-/-

Fig. 1C

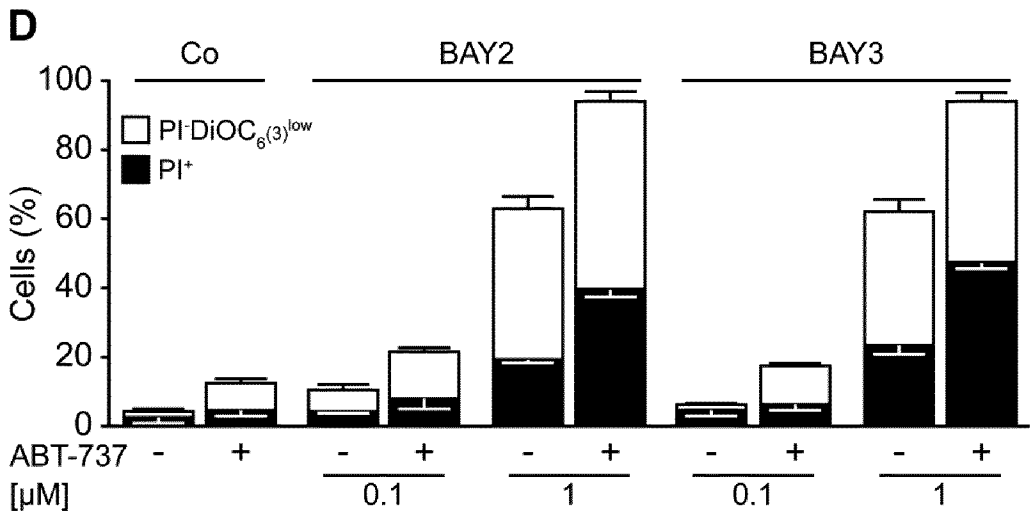

D
Co
BAY2
BAY3
100
80
60
40
20
0
PI-DiOC6(3)low
PI+
Cells (%)
ABT-737 - + - + - + - + - +
[µM] 0.1 1 0.1 1

Fig. 1D

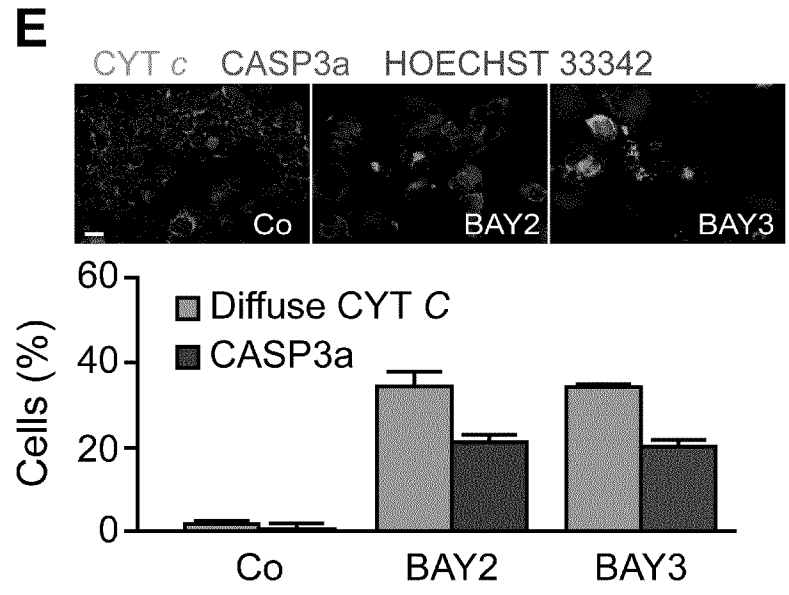

E
CYT c CASP3a HOECHST 33342
Co
BAY2
BAY3
60
40
20
0
Diffuse CYT C
CASP3a
Cells (%)
Co
BAY2
BAY3

Fig. 1E

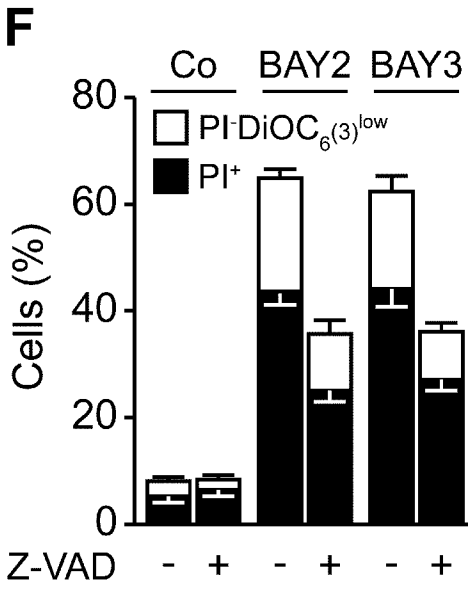



Fig. 1F

# INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/066035

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/495 A61K31/5025 A61K45/06
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 13 November 2013 | 21/11/2013 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Steendijk, Martin |

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