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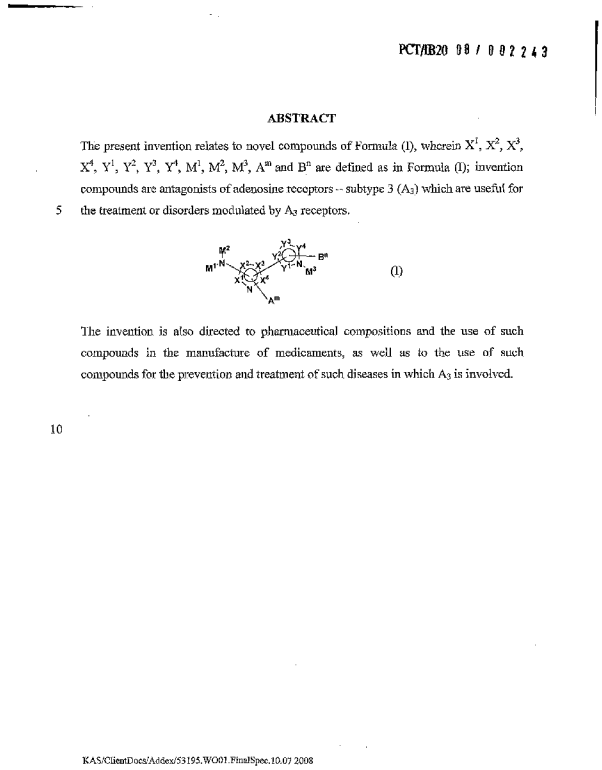
(54) Title: NOVEL HETEROARYL DERIVATIVES AS ANTAGONISTS OF ADENOSINE A3 RECEPTOR



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ABSTRACT

The present invention relates to novel compounds of Formula (I), wherein X^1, X^2, X^3, X^4, Y^1, Y^2, Y^3, Y^4, M^1, M^2, M^3, A^m and B^n are defined as in Formula (I); invention compounds are antagonists of adenosine receptors -- subtype 3 (A_3) which are useful for the treatment or disorders modulated by A_3 receptors.

(I)

The invention is also directed to pharmaceutical compositions and the use of such compounds in the manufacture of medicaments, as well as to the use of such compounds for the prevention and treatment of such diseases in which A_3 is involved.

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(57) **Abstract:** The present invention relates to novel compounds of Formula (I), wherein X^1, X^2, X^3, X^4, Y^1, Y^2, Y^3, Y^4, M^1, M^2, M_3, A^m and B^n are defined as in Formula (I); invention compounds are antagonists of adenosine receptors - subtype 3 (A_3) which are useful for the treatment or disorders modulated by A_3 receptors. The invention is also directed to pharmaceutical compositions and the use of such compounds in the manufacture of medicaments, as well as to the use of such compounds for the prevention and treatment of such diseases in which A_3 is involved.

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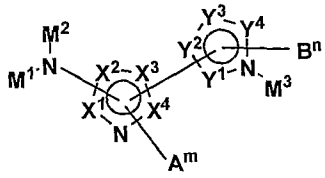

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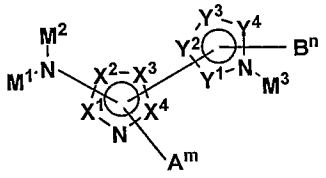
The invention is also directed to pharmaceutical compositions and the use of such compounds in the manufacture of medicaments, as well as to the use of such compounds for the prevention and treatment of such diseases in which A_3 is involved.

NOVEL HETEROARYL DERIVATIVES AS ANTAGONISTS OF ADENOSINE A3 RECEPTOR

SUMMARY OF THE INVENTION



(I)

The present invention relates to novel compounds of Formula (I), wherein X^1, X^2, X^3, X^4, Y^1, Y^2, Y^3, Y^4, M^1, M^2, M^3, A^m and B^n are defined as in Formula (I); invention compounds are antagonists of adenosine receptors – subtype 3 (A_3) which are useful for the treatment or prevention of disorders modulated by A_3 receptors. The invention is also directed to pharmaceutical compositions and the use of such compounds in the manufacture of medicaments, as well as to the use of such compounds for the prevention and treatment of such diseases in which A_3 receptor is involved.

BACKGROUND OF THE INVENTION

The extracellular purine nucleoside adenosine is present in all tissues and body fluids and is known to function as a modulator of a variety of physiological processes.

One of the primary roles of adenosine is cytoprotection against ischemia-induced cell damage, mainly in tissues such as the heart, brain and kidney, which are especially prone to ischemic injury (Mubagwa and Flameng (2001) Cardiovasc. Res. 52:25-39). The effects of adenosine on tissue protection and repair include increasing the ratio of oxygen supply to demand, protecting against ischemic damage by cell conditioning, triggering anti-inflammatory responses and promoting angiogenesis. Other actions of adenosine include the regulation of cellular growth and differentiation, vasodilatation

and blood flow control, inflammatory responses, central and peripheral neural function, neuroprotection and apoptosis (see in Bruns (1990) Ann NY Acad Sci. 603:211-225; for a recent review see Gao and Jacobson (2006) Nat Rev Drug Discov. 5:247-64).

Adenosine levels in tissues change with cellular activity and energy demand and the sources of adenosine are either release through an equilibrative transporter or as a result of cell damage (McGaraughty et al (2005) Curr. Top.Med. Chem. 5, 43–58), or nucleotidase-mediated hydrolysis of extracellular adenine nucleotides (Zimmermann (2000) Naunyn Schmiedebergs Arch. Pharmacol. 362:299–309), which have their own signalling properties that are mediated by purinergic P2 receptors. Adenosine itself is rapidly metabolized by adenosine kinase (Parkinson et al (2005) Neurol. Res. 2:153–160) and, to a lesser extent, adenosine deaminase to AMP and inosine, respectively, both of which are less active than adenosine on adenosine receptors (ARs). AR action also might be modulated by inhibition of the metabolism of extracellular adenosine (Parkinson et al (2005) Neurol. Res. 2:153–160) or its cellular uptake by adenosine transporter (McGaraughty et al (2005) Curr. Top.Med. Chem. 5:43–58). Under metabolic stress conditions extracellular concentrations of adenosine and its metabolites inosine, hypoxanthine, and xanthine increase dramatically, mainly through breakdown of adenosine triphosphate (Roth et al (1997) Exp. Eye Res. 65:771-779; Von Arnim et al (2000) Neuroreport. 11:1223-1226; Ramkumar et al (2001) Jpn J Pharmacol. 86:265-274).

The protective effects are mediated by activation of four pharmacologically and biochemically distinct adenosine receptors, named A_1, A_{2A}, A_{2B}, and A_3, which belong to the family of G-protein-coupled receptors and that have been cloned from several mammalian and non-mammalian species, including man (see Nomenclature and Classification of adenosine receptors from the International Union of Basic and Clinical Pharmacology (IUPHAR): Fredholm et al (2001) Pharmacol Rev 53:527–552). The A_1 and A_3 receptor subtypes couple to Gi-protein, mediating the inhibition of adenylyl

cyclase and a decrease in cAMP levels, whereas the A_{2A} and A_{2B} receptors activate adenylyl cyclase and increase cAMP levels via stimulatory Gs-protein.

Among the human ARs, the most similar are the A_1 and A_3 ARs (49% sequence similarity) and the A_{2A} and A_{2B} ARs (59% similarity). Although the degree of homology is somewhat low, it has been very difficult to develop highly selective or even specific adenosine receptor subtype agonists and antagonists. There is high sequence similarity between species for the A_1, A_{2A} and A_{2B} receptors, whereas A_3 receptors are more variable.

The modulation of adenosine receptors may be useful for therapeutic intervention due to their distribution in several types of tissue throughout the body. Many pathological conditions such as renal failure, cardiac and cerebral ischemia, central nervous system disorders, neurodegenerative diseases and inflammatory pathologies may be treated with selective modulators of the different sub-types of adenosine receptors (for a review see Gao and Jacobson (2006) Nat Rev Drug Discov. 5:247-64).

The adenosine A_3 receptor (A_3AR) is the most recently discovered adenosine receptor (Zhou et al (1992) Proc Natl Acad Sci U S A. 89:7432-6; Salvatore et al (1993) Proc Natl Acad Sci U S A. 90:10365-9). In addition to Gi protein, the A_3AR couples to second-messenger pathways resulting in stimulation of phospholipase C (PLC) (Abbracchio et al. (1995) Mol. Pharmacol. 48:1038–1045) and calcium mobilization via a Gi/o-dependent pathway (Shneyvays et al (2005) Am. J. Physiol. Heart Circ. Physiol. 288 :H2792–H2801; Englert et al (2002) Biochem. Pharmacol. 64:61–65; Fossetta et al (2003) Mol. Pharmacol. 63:342–350; Shneyvays et al (2004) Cell Calcium 36:387–396). In cardiac cells, A_3AR agonists induce protection through the activation of KATP channels (30). RhoA–phospholipase D1 signaling has been demonstrated to mediate the anti-ischemic effect of A_3ARs (Mozzicato et al (2004)

FASEB J. 18:406–408.). The WNT signaling pathway is involved in A_3AR agonist-mediated suppression of melanoma cells (Fishman et al (2002) Oncogene 21:4060–4064.). In addition, like other ARs, the A_3AR couples to MAPK, which suggests a possible role in cell growth, survival, death and differentiation (Schulte & Fredholm (2002) Mol. Pharmacol. 62:1137–1146; Schulte & Fredholm (2003) Cell Signal. 15:813–827). An A_3AR agonist inhibits proliferation in A375 human melanoma cells via the phosphatidylinositol 3-kinase–protein kinase B–ERK1/2 pathway (Merighi et al. (2005) J. Biol. Chem. 280:19516-19526). It is suggested that the adenosine A_3 receptor activates ERK1/2 in human fetal astrocytes (Neary et al (1998) Neurosci Lett.; 242:159-62) and in CHO cells (Schulte and Fredholm (2000) Mol Pharmacol. 58:477-82). The A_3 receptor agonists Cl-IB-MECA and IB-MECA have been reported to potently inhibit and less potently to activate apoptosis in various cells (Abbracchio et al (1997) Ann NY Acad Sci 825:11–22). In RBL-2H3 mast-like cells, Cl-IB-MECA potently blocks UV irradiation-induced apoptosis by a process correlated with protein kinase B phosphorylation which is blocked by pertussis toxin and wortmannin (Gao et al (2001) Mol Pharmacol 59:76–82).

The use of more selective pharmacological tools for the A_3AR has led to a better understanding of the functions of the receptor. The A_3AR selective agonists IB-MECA and Cl-IB-MECA have been used extensively as pharmacological probes in the elucidation of the physiological roles of this receptor (Jacobson (1998) Trends Pharmacol. Sci. 19:184–191). However, much less is known about the effects of antagonists of A_3ARs in part because the classical xanthine class antagonists of A_1, A_{2A} and A_{2B} ARs (e.g., caffeine and theophylline) have low binding affinities for the rat A_3AR (Zhou (1992) Proc. Natl Acad. Sci. USA 89:7432–7436). In general, there is a higher affinity for the human A3 receptor as compared to the rat receptor for the different class of purine or non-purine like A_3AR antagonists available including, among many, xanthine, adenine derivatives, imidazo[2,1-i]purin-5-ones, quinazolines and derivatives, 1,4-dihydropyridines and pyrans, pyrimidines derivatives (Zhou (1992) Proc. Natl Acad. Sci. USA 89:7432–7436; Yang (2005) Curr.Eye Res. 30:747–754;

Müller, C. et al. (2001) Mini Reviews in Medicinal Chemistry 1:339-348). Therefore, the search for A_3AR antagonists turned towards more novel heterocyclic systems (Jacobson (1998) Trends Pharmacol. Sci. 19:184–191) and screening of diverse chemical libraries resulted in the identification of new high-affinity non-xanthine compounds for the human A_3AR, including 1,4-dihydropyridine, flavonoids, pyridines, thiazoles, triazoloquinazoline, isoquinoline and quinazoline, isoquinoline and quinazoline derivatives among others (Baraldi et al (2000) Med Res Rev. 20:103–128; Gao and Jacobson (2006) Nat Rev Drug Discov. 5:247-64). Although potency and selectivity towards human adenosine A_3ARs have been improved in these novel heterocyclic compounds, the overall profile has not improved sufficiently to consider development in human beings. Some high-affinity derivatives of adenosine with added substituents or rigidified derivates of adenosine improve the affinity at the target but in both cases the overall profile of ligands is far from optimal, as pharmacokinetic properties remain poor. The conformationally constrained nucleoside MRS1292, which is a selective A_3AR antagonist, in both rat and human (Gao et al. (2002) J. Med. Chem. 45:4471–4484; Yang et al (2005) Curr. Eye Res. 30:747–754) is currently used in vitro as a reference antagonist.

Adenosine A_3 receptors are found mostly in brain, lung, liver, heart, kidney and testis (Gao and Jacobson (2006) Nat Rev Drug Discov. 5:247-64) and have been implicated in cell cycle progression and cell growth (Brambilla et al. (2000) Naunyn Schmiedebergs Arch Pharmacol. 361:225-34), modulation of apoptosis (Abbracchio et al. (1997) Biochem Biophys Res Commun. 241:297-304), cancer (Baraldi et al (2005) Curr Med Chem. 12:1319-29), mast cell degranulation (Jin et al. (1997) J Clin Invest. 100:2849-57), cardiac ischemia and ischemic pre-conditioning in the heart (Strickler et al., (1996) J Clin Invest. 98:1773-9), neuroprotection (see in Fredholm (1997) Int Rev Neurobiol. 40:259-80), pro- and anti-inflammatory modulation (Salvatore et al. (2000) J. Biol. Chem. 275:4429-4434), asthma (Jacobson et al (1998) Drug Dev. Res. 45:113), neurodegeneration (Jacobson et al (1995) Drugs Future 20:689 ; Kohno et al (1996) Blood 88: 3569), ischemic brain damage (Von Lubitz et al (1994) Eur. J. Pharmacol.

263:59; Von Lubitz et al (1999) Eur. J. Pharmacol. 367:157) and hypotension (Hannon et al (1995) Br. J. Pharmacol. 115:945). In addition, adenosine A_3 receptors have functional effects that are dependent on the degree of receptor activation. Specifically, when activated moderately, A_3ARs have a cytoprotective role for example reducing damage to heart cells from lack of oxygen or protecting cells from apoptosis. Indeed moderate activation of the A_3 receptor is known to activate the cellular antioxidant defense system by increasing the activities of superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase, along with a reduction in malondialdehyde, a marker of lipid peroxidation (Maggirwar et al (1994) Biochem Biophys Res Commun 201:508-512). Such a mechanism may provide a mechanism by which adenosine exerts a cytoprotective action in ischemic conditions. However, high levels of A_3AR stimulation can actually result in cell death. This could be linked to the observation that there is a subsequent upregulation of selective A_3 receptor observed, for instance, by RBL-2H3 cells in vitro after exposure to oxidative stress (Ramkumar et al (2001) Jpn J Pharmacol 86:265-274) and after preconditioning of central nervous tissue, whereas expression of A_1, A_{2A} and A_{2B} ARs remained unchanged (Von Arnim et al (2000) Neuroreport 11:1223-1226). Excessive A_3AR activation is toxic for the cells. Indeed A_3ARs modulators are being tested for therapeutic potential, for example, treatment of cancer, heart conditions, neurological conditions, pain, asthma, inflammation, glaucoma and other immune implications. In particular, there are literature data strongly suggesting that a A_3R antagonist may be used specifically in the treatment of several conditions as listed below:

A role for the A_3AR in mediating control of the cell cycle has been reported (Neary et al (1998) Neurosci. Lett 242:159-162). For example, there is a significant over-expression of A_3ARs in several types of tumor cells (Madi et al (2004) Clin. Cancer Res. 10:4472-4479; Gessi et al (2004) Clin. Cancer Res. 10:5895-5901). A_3AR antagonists might sensitize tumor cells to chemotherapeutic drugs as it is known that A3 receptor subtype activation plays a role in the prosurvival and in the antiapoptotic effect of adenosine (Merighi et al (2003) Biochem. Pharmacol. 66:739-748; Baraldi et

al (2005) Curr. Med Chem 12:1319-1329). An opportunity would be then that A_3AR antagonists might sensitize tumors cells to chemotherapeutic drugs and therefore could inhibit tumor growth and metastasis in patient. Possible indication therefore for selective adenosine A_3 antagonists is the use of such compounds class in synergistically improving chemotherapeutic treatment of cancers expressing A_3ARs and cancers expressing P-glycoprotein or MRP in combination with other anti-tumor agents such as antiangiogenic agents and/or cytostatic agents.

The adenosine A_3 receptor was initially implicated as the receptor subtype that triggers the degranulation of rat RBL 2H3 mast-like cells (Ramkumar et al., 1993) and perivascular mast cells of the hamster cheek pouch (Jin et al (1997) J Clin Invest. 100:2849-57) and therefore A_3AR has been implicated in mediating allergic responses: A_3 receptor agonists induce mast cell degranulation and consequent release of allergic mediators, such as histamine, when administered to rats or mice (Ramkumar et al (1993) J. Biol. Chem. 268:16887–16890; Tilley et al (2000) J Clin Invest.105:361-7). Systemic infusion in mice of IB-MECA causes scratching that is prevented by co-administration of histamine antagonists. In contrast, in mice lacking A_3ARs (Salvatore et al (2000) J. Biol. Chem 275:4429-4434), the potentiation by Cl-IB-MECA of antigen-dependent degranulation of mast cells, as measured by hexosaminidase release, was lost and lipopolysaccharide-induced tumour-necrosis factor-α (TNFα) production was lower than in control mice (Salvatore et al (2000) J. Biol. Chem 275:4429-4434). The effect of adenosine analogs on mast cell degranulation (Salvatore et al (2000) J. Biol. Chem 275:4429-4434) and the consequent decrease in vascular permeability (Tilley et al (2000) J Clin Invest.105:361-7) is decreased in mice with a targeted disruption of the A_3AR receptor. Taken together, these observations suggest that A_3AR receptor antagonists have the potential for treating diseases and disorders resulting from or including a component of inflammation. This could be extended to the treatment of asthma and others respiratory diseases involving inflammation and or allergenic responses. In the asthmatic lung, adenosine acts as an irritant and bronchoconstrictor, suggesting that a synthetic A_3AR antagonist, could have therapeutic potential in asthma

treatment (Holgate (2005) Br. J. Pharmacol 145:1009-1015). In patients with asthma, relatively high density of functionally active A_3 receptors are expressed in human eosinophils (Kohno et al (1996) Blood 88:3569-74) and appear to be involved in the inhibition of eosinophil chemotaxis when stimulated (Walker et al (1997) Am J Respir Cell Mol Biol 16:531-7). Since inflammation in allergic rhinitis is characterized by eosinophilic infiltration of the airways, it is possible that the elevated adenosine concentrations associated with allergic inflammation would contribute to inhibition of mucosal inflammation through stimulation of eosinophils-expressed A_3 receptors (Rimmer et al (2007) Clin Exp Allergy; 37:8-14). A recent clinical trial has shown that a novel dual agonist of A_2ARs and antagonist of A_3ARs appears to have some clinical benefit in both the early-phase and the late-phase response to intranasal allergen challenge. Notably, there was a reduction of some pro-inflammatory mediators suggesting that comparable, more selective compounds of A_2AR or A_3ARs may have additional benefits (Rimmer et al (2007) Clin Exp Allergy 37:8-14).

A_3ARs antagonists may be useful for the acute and chronic treatment of glaucoma and other visual disorders in general. Glaucoma is characterized by elevated intraocular pressure (IOP) and is a leading cause of irreversible blindness. Molecular and pharmacological studies have provided evidence that all adenosine receptor subtypes are expressed in ocular tissues (Blazynski et al (1992) J Neurochem. 58:761– 767; Wax et al (1993) Exp Eye Res. 57:89 –95 ; Wax et al (1994) Invest Ophthalmol Vis Sci. ;35:3057–3063 ; Kvanta et al (1997) Exp Eye Res. 65:595–602 ; Fleischhauer et al (2003) J Membr Biol. 193:121–136.) and that activation of these receptors has been shown to regulate retinal neurotransmission and neuroprotection (Blazynski et al (1992) J Neurochem. 58:761– 767; Macaluso et al (2003) Doc Ophthalmol. 106: 51–59) retinal and choroidal blood flow (Braunagel et al (1988) J Ocul Pharmacol. 4:61–73), photoreceptor phagocytosis (Gregory et al (1994) Invest Ophthalmol Vis Sci. 35:819–825) and integrity of the blood–retinal barrier (Sen et al (1989) Arch Ophthalmol. 107:1364–1367; Campochiaro et al (1989) Arch Ophthalmol. 107:412–416). The adenosine system has also been shown to regulate ion transport in corneal

(Riley et al (1996) Invest Ophthalmol Vis Sci. 37:1–10.) and ciliary epithelia (Carre et al (1997) Am J Physiol. 273:C1354–C1361; Mitchell et al (1999) Am J Physiol. 276:C659–C666) and to modulate aqueous humor in- and outflow (Crosson (1995) J Pharmacol Exp Ther. 273:320–326; Crosson and Gray (1996) Invest Ophthalmol Vis Sci. 37:1833–1839; Tian et al (1997) Exp Eye Res. 64:979–989).

In pathophysiological conditions, adenosine and its receptors have been implicated in many ocular and systemic ischemic diseases such as retinal ischemia and in conditions with oxidative stress in rodents (Roth S et al (1997) Exp Eye Res. 65:771–779; Lutty and Mc Leod (2003) Prog Retin Eye Res. 22:95–111, Larsen and Osbourne (1996) Invest Ophthalmol Vis Sci. 37: 2603–2611). Civan and co-workers have found that the A_3 adenosine receptors regulate Cl(-) channels of non-pigmented ciliary epithelial cells (Von Arnim et al (2000) Neuroreport. 11:1223-1226). Furthermore, the knock-out of A_3ARs gene in the mice or their pharmacological blockage with selective antagonists in normal mice with MRS 1191, MRS 1097, and MRS 1523 lowered IOP (Ramkumar et al (2001) Jpn J Pharmacol. 86:265–274; Safran et al (2001) Mol Cell Biochem. 217:143–152). These results suggest that antagonists of A_3ARs may provide a novel approach for the treatment of glaucoma (Fredholm et al (2001) Pharm Rev. 53:527–552). This has extended in vitro observations implicating A_3 receptors in tissues controlling aqueous humour physiology (Fredholm et al (2001) Pharm Rev. 53:527–552). In contrast, A_3 agonists have been shown to activate chloride channels in non pigmented ciliary epithelial cells in vitro, leading to the hypothesis that A_3 receptor agonists would increase aqueous humor secretion and thereby IOP in vivo (Mitchell et al (1999) Am J Physiol. 276:C659–C666).

The cross-species A_3AR antagonist MRS1292 was recently found to reduce mouse intraocular pressure but also inhibited adenosine-triggered human non-pigmented ciliary epithelial cell fluid release (Yang, H. et al (2005) Curr. Eye Res. 30: 747–754). OT-7999, a potent and selective A(3) receptor antagonist administered via topical eye-

drops was found to significantly decrease intraocular pressure in monkey without ophthalmologic side effects, such as appearance of eyelid closure, hyperemia of the external and anterior ocular segments or abnormality of the pupil (Okamura et al (2004) Bioorg. Med. Chem. Lett. 14: 3775–3779).

In human, the A_3 receptor subtype has been immunolocalized to the basolateral surface infoldings of non-pigmented ciliary epithelial cells, which is consistent with the receptor's functional role in aqueous humor secretion. In ocular hypertensive individuals, the mean aqueous adenosine levels were significantly elevated when compared to normotensive subjects and correlated with IOP levels (Daines et al (2003) J Ocul Pharmacol Ther. 19:113–119). However, in the eyes of healthy subjects, parenteral infusion of adenosine induced a small but significant decrease in IOP (Polska et al (2003) Invest Ophthalmol Vis Sci. 44:3110–3114). An involvement of the adenosine system in ischemia/hypoxia and IOP elevation in pseudoexfoliation (PEX) eye syndrome, a common age-related extracellular matrix disorder that often leads to the development of ocular hypertension and secondary open-angle glaucoma, may therefore be hypothesized. A recent study further provided evidence of a selective and significant upregulation of the A_3 adenosine receptor on both the mRNA and protein levels, in the non-pigmented ciliary epithelium of all patients eyes with PEX syndrome confirming a previous study showing a 30-fold overexpression of A_3 adenosine receptor mRNA in the ciliary processes of PEX eyes compared with control eyes (Schlötzer-Schrehardt et al (2004) IOVS 45: ARVO E-Abstract 3535).

This finding suggested that hypoxia and/or oxidative stress, typical of all eyes with PEX syndrome/glaucoma (Ritch and Schlötzer-Schrehardt (2001) Surv Ophthalmol. 45:265–315; Helbig et al (1994) German J Ophthalmol. 3:148 –153) promotes a selective upregulation of A_3 adenosine receptors in non-pigmented ciliary epithelium, which may confer protection against ischemic or oxidative damage to sustain prolonged periods of chronic hypoxia or oxidative stress. Considering, however, the known

properties of the A_3 receptor in activating chloride transport in epithelial cells, its upregulation in the nonpigmented ciliary epithelium may have an additional influence on aqueous humor secretion and hence on IOP levels in PEX eyes. It has been previously reported that IOP elevation in PEX patients results from an increased outflow resistance in the trabecular meshwork, whereas the rate of aqueous flow through the anterior chamber was not different or even slightly lower in PEX eyes than in control eyes (Johnson and Brubaker (1982) Am. J. Ophthalmol. 93:629–634).

These results above mentioned suggest that antagonists of A_3ARs may be useful for the acute and chronic treatment of glaucoma and other visual disorders in general. International patent publication WO 00/03741 describes a method for decreasing intraocular pressure by administering an A_3 adenosine receptor antagonist.

All of these finding could be of clinical and therapeutic significance and the reduction of chloride channel activity with A_3 receptor antagonists if confirmed in human beings may be an alternative specific approach for treating ocular hypertension in patients, for example, with PEX who are refractory to standard medical therapy. Patients with glaucoma may require long-term administration of IOP-lowering medications. These medications belong to several classes of molecules including beta-adrenergic blockers, prostaglandin receptor inhibitors, cholinergic agents, alpha-adrenergic agonists, carbonic anhydrase inhibitors, and ocular hypotensive lipids and are associated with mild and ocular side-effects. However, several of them are associated with systemic risks as well as serious ocular effects, especially following chronic use (Roth et al (1997) Exp. Eye Res. 65:771–779).

Recent evidence suggested that both A_1AR agonists and A_3AR antagonists protect the kidney. Precisely, mice lacking A_3ARs or wild-type mice in which the A_3AR was blocked pharmacologically had significant renal protection (Lee et al (2003) Am. J.

Physiol. Renal. Physiol. 284: F267-F273), suggesting that A_3AR antagonists might have general renal-protective properties. Ligands possessing dual acting and opposite properties at these AR subtypes could therefore be effective therapeutic agents for renal protection.

A_3 receptor has been mainly implicated in ischemic disease, such as ischemic brain damage or cardiac ischemia (Baraldi et al (2003) Eur. J. Med. Chem. 38:367–382). Adenosine is released in large amounts during myocardial ischemia, resulting in effective preconditioning in cardiomyocytes through the activation of A_1 and A_3 ARs (Shneyvays et al (2004) Cell Calcium 36:387–396; Tracey et al (1998) Cardiovasc. Res. 40:138–145 ; Mozzicato et al (2004) FASEB J. 18: 406–408; Auchampach (1997) Circ. Res. 80: 800–809). AR agonist to activate either or both of these receptors might therefore be beneficial to the survival of the ischemic heart. Various lines of evidence indicate that the A_3AR has a role in protecting the heart (Auchampach (1997) Circ. Res. 80: 800–809; Tracey et al (2003) Am. J. Physiol. Heart Circ. Physiol. 285:H2780–H2787). Overexpression of A_3ARs decreases heart rate, preserves energetics and protects ischemic heart (Cross et al (2002) Am. J. Physiol. Heart Circ. Physiol. 283:H1562–H1568) and low-level expression of A_3ARs in the heart provides effective protection against ischemic injury without detectable adverse effects, although higher levels of A_3AR expression lead to the development of a dilated cardiomyopathy (Black et al (2002) Circ. Res. 91:165–172). As said earlier, this could be not good during too long activation. And paradoxically, global deletion of the A_3AR in mice also confers resistance to myocardial ischaemic injury and does not prevent early preconditioning (Guo et al (2001) J. Mol. Cell Cardiol. 33:825–830). In an isovolumic Langendorff perfusion model, A_3AR-knockout mice also had improved functional recovery and tissue viability during reperfusion after ischemia when compared with control mice (Tracey et al (2003) Am. J. Physiol. Heart Circ. Physiol. 285:H2780–H2787).

Using rat basophilic leukemia 2H3 cell line (RBL-2H3), it has been established that activation of A_3ARs stimulates SERT activity via both PKG and p38 MAPK (Zhu et al (2004) Mol Pharmacol. 65:1462-74). Therefore, as it is known that the inactivation of synaptic serotonin (5-hydroxytryptamine, 5-HT) is primarily through reuptake by the presynaptic, 5-HT transporter (SERT, SLC6A4), it is likely that A_3AR antagonists could be interesting in treating pathologies resulting from a low level of serotonin (including affective disorders including depression and depressive disorders, anxiety disorders including obsessive-compulsive disorder, post-traumatic stress disorder, panic disorder and phobias, borderline personality disorder, anorexia nervosa, bulimia nervosa, autism, attention deficit hyperactivity disorder, Tourette's syndrome, sexual disorders, migraine, diabetic neuropathy, obesity, drug or alcohol addiction, sleep disorders, arthritis, chronic fatigue syndrome or irritable bowel syndrome) because such compounds will decrease the SERT surface expression and/or catalytic rates.

In conclusion, and considering hypotheses based on the known distribution of A_3ARs. its in vitro functional role and the knowledge of its role in physiological and pathological conditions from preclinical and clinical data, together with the use of subtype selective A_3ARs antagonists, it is foreseen that the blockade of A_3ARs could be a valuable approach to treat eye disorders including glaucoma and related conditions, inflammatory processes including allergy, asthma and airway pathologies, ischemic brain and cardiac diseases and related, renal dysfunction, tumor and abnormal cell growth, and depression, anxiety and related neuropsychiatric and affective disorders.

The following compounds are known:

(i) International patent publication WO2001/64674, as well as US patent publications US2003/0203897 and US7105550, describe 2,4-disubstituted thiazolyl derivatives, such as N-phenyl-4-(1H-pyrazol-3-yl)thiazol-2-amine hydrobromide [358779-21-2], for the prevention or the treatment of disease throught cytokines, in

particular, Tumor Necrosis Factor-Alpha (TNF-α) and Interleukin-12 (IL-12) or throught activation of Adenosine A_3 receptor;

International patent publication WO2006/122011 describes thiazole derivatives, such as 4-(2-(4-(octyloxy)-3-(trifluoromethyl)phenylamino)thiazol-4-yl)-1*H*-pyrazole-3-carbonitrile [914668-55-6] as Hepatite C Virus replication inhibitors;

(ii) International patent publication WO2006/069155 describes (S)-2-amino-N-(3-(1H-pyrazol-1-yl)benzyl)propanamide derivatives, such as (2S)-2-amino-N-(3-(5-(5-(phenylamino)-1,3,4-oxadiazol-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzyl)-propanamide [895524-13-7], as protein arginine methyl transferase inhibitors;

(iii) International patent publication WO2005/112923 describes 5-anilino-4-heteroarylpyrazole derivatives, such as 5-methoxy-2-([1-(2-methoxyphenyl)-1',3-dimethyl-1H,1'H-4,4'-bipyrazol-5-yl]amino)benzoic acid [870188-47-9], useful for the treatment of diabetes or related disorders;

(iv) International patent publication WO2005/125101 describes imidazopyrazine derivatives such as (Z)-5-(3-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyrazin-2-ylamino)-2,3-dihydro-1H-inden-1-one oxime [915705-05-4] as RAF kinase inhibitors;

(v) Some (5-methyl-1-phenyl-1H-pyrazol-4-yl)thiazol-2-amino derivatives have been reported: Singh, S.P. et al. (1997) J: Indian Chem. Soc. (74, 11-12): 940-942 described a synthetic route from 4-acylpyrazole, using [hydroxyl(tosyloxy)iodo]benzene; US patent publication US7244739 describes compounds as Amyloid-beta (Aβ) modulators useful for the treatment of neurodegenerative disorders;

(vi) Hassan, N.M. et al (1997) J. Chem. Res., Syn. (10): 350-351 described a synthetic route to obtain 4-((1-aryl-4-carbonitrile-5-phenyl)-1H-pyrazolyl)-2-aminophenyl thiazoles;

(vii) International patent publication WO 99/64418 describes arylpyridinyl thiazoles as adenosine receptor antagonists, such as 4-(4-methoxyphenyl)-N-(pyridin-2-yl)-5-

(pyridin-4-yl)thiazol-2-amine or N-(5-(pyridin-4-yl)-4-(3,4,5-trimethoxyphenyl)thiazol-2-yl)acetamide, having activity at the A_3 and/or A_{2B} receptors;

Press, N.J. et al (2004) Curr. Topics Med. Chem. (4): 863-870 described arylpyridinyl thiazoles, such as N-(5-(pyridin-4-yl)-4-(3,4,5-trimethoxyphenyl)thiazol-2-yl)acetamide, having adenosine A_3 receptor antagonism properties, useful as pharmacological tools;

European patent publication EP1027050 and US patent publication US6620825 describe 1,3-thiazoles as adenosine A_3 receptor antagonist for the treatment of allergy, asthma and diabetes, such as compounds substituted at the 4- or 5-position, or both, by a pyridyl, such as 4-(4-methoxyphenyl)-N-phenyl-5-(pyridin-3-yl)thiazol-2-amine or 4-(4-methoxyphenyl)-N,5-di(pyridin-3-yl)thiazol-2-amine;

(viii) International patent publication WO 02/42298 as well as Press, N.J. et al (2005) Bioorg. Med. Chem. Lett. (15): 3081-3085 described aminothiazoles, such as 3-(5-(1H-imidazol-1-yl)-2-(6-methylpyridin-2-ylamino)thiazol-4-yl)benzonitrile, having adenosine receptor antagonism properties, particularly at the A_3 and A_{2B} receptors, and useful for the treatment of inflammatory or obstructive airways diseases;

(ix) Borghini, A. et al. (2005) Bioorg. Med. Chem. Lett. (13): 5330-5337 described thiazole and thiadiazole derivatives, such as 4-hydroxy-N-(3-phenyl-1,2,4-thiadiazol-5-yl)benzamide or N-(3-(4-methoxyphenyl)-1,2,4-thiadiazol-5-yl)acetamide, having adenosine A_1 or A_3 receptors antagonism properties.

(x) International patent publication WO2007/031440 describes 2-aniline-4-aryl substituted thiazole as positive modulators of nicotinic acetylcholine receptors;

(xi) Japan patent application JP2003313176 describes 2-aminothiazole derivatives having cell proliferation inhibitory activity for preventing and treating cancer.

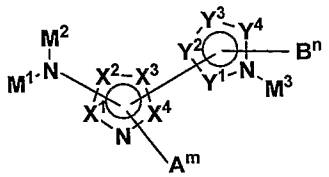
It has now surprisingly been found that the compounds of general formula (I), (II), (III), (IIIA) and (IIIB) show potent activity and subtype-selectivity on Adenosine A_3 receptor. The compounds of the invention demonstrate advantageous properties over

compounds of the prior art, noteworthy selectivity versus the other adenosine receptor subtypes such as A_1 receptor, A_{2A} receptor and A_{2B} receptor.

The present invention relates to a method of treating or preventing a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of Adenosine A3 receptor antagonists.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to compounds having A_3 receptor antagonist activity. In its most general compound aspect, the present invention provides a compound according to Formula (I),



(I)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof, wherein:

X^1, X^2, X^3 and X^4 are each independently selected from the group of C, N, O, S and C=C representing a 5 or 6 membered heteroaryl ring which may further be substituted by 1 to 3 radicals A^m;

m is an integer ranging from 1 to 3;

A^m radicals are each independently selected from the group of hydrogen, halogen, -CN, $-CF_3$, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylcyano, -(C_1-C_6)alkylheteroaryl, -(C_1-C_6)alkylaryl, aryl, heteroaryl, heterocycle, -(C_0-C_6)alkyl-OR^1, -O-(C_2-C_6)alkyl-OR^1, -NR^1(C_2-C_6)alkyl-OR^2, -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -O-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -NR^1-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo-OR^1, -(C_1-C_6)alkylhalo-NR^1R^2, -(C_0-C_6)alkyl-S-R^1, -O-(C_2-C_6)alkyl-S-R^1, -NR^1-(C_2-C_6)alkyl-S-R^2, -(C_0-C_6)alkyl-S(=O)-R^1, -O-(C_1-C_6)alkyl-S(=O)-R^1, -NR^1-(C_1-C_6)alkyl-S(=O)-R^2, -(C_0-C_6)alkyl-$S(=O)_2$-R^1, -O-(C_1-C_6)alkyl-$S(=O)_2$-R^1, -NR^1-(C_1-C_6)alkyl-$S(=O)_2$-R^2, -(C_0-C_6)alkyl-NR^1R^2, -O-(C_2-C_6)alkyl-NR^1R^2, -NR^1-(C_2-C_6)alkyl-NR^2R^3, -(C_0-C_6)alkyl-$S(=O)_2NR^1R^2$, -O-(C_1-C_6)alkyl-$S(=O)_2NR^1R^2$, -NR^1-(C_1-C_6)alkyl-$S(=O)_2NR^2R^3$, -(C_0-C_6)alkyl-NR^1-$S(=O)_2R^2$, -O-(C_2-C_6)alkyl-NR^1-$S(=O)_2R^2$, -NR^1-(C_2-C_6)alkyl-NR^2-$S(=O)_2R^3$, -(C_0-C_6)alkyl-C(=O)-NR^1R^2, -O-(C_1-C_6)alkyl-C(=O)-NR^1R^2, -NR^1-(C_1-C_6)alkyl-C(=O)-NR^2R^3, -(C_0-C_6)alkyl-NR^1C(=O)-R^2, -O-(C_2-C_6)alkyl-NR^1C(=O)-R^2, -NR^1-(C_2-C_6)alkyl-NR^2C(=O)-R^3, -O-(C_2-C_6)alkyl-OC(=O)-R^1, -NR^1-(C_2-C_6)alkyl-OC(=O)-R^2, -(C_0-C_6)alkyl-C(=O)-OR^1, -O-(C_1-C_6)alkyl-C(=O)-OR^1, -NR^1-(C_1-C_6)alkyl-C(=O)-OR^2, -(C_0-C_6)alkyl-C(=O)-R^1, -O-(C_1-C_6)alkyl-C(=O)-R^1, -NR^1-(C_1-C_6)alkyl-C(=O)-R^2, -(C_0-C_6)alkyl-NR^1-C(=O)-OR^2, -(C_0-C_6)alkyl-NR^1-C(=O)-NR^2R^3, -O-(C_2-C_6)alkyl-NR^1-C(=O)-NR^2R^3, and -NR^1-(C_2-C_6)alkyl-NR^2-C(=O)-NR^3R^4;

Any two radicals of A^m (A^1 and A^2) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

R^1, R^2, R^3 and R^4 are each independently hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)alkylcyano, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl;

Any two radicals of R (R^1, R^2, R^3 or R^4) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

Y^1, Y^2, Y^3 and Y^4 are each independently selected from the group of C and N representing 5 membered heteroaryl ring which may further be substituted by 1 to 3 radicals B^n;

n is an integer ranging from 1 to 3;

B^n radicals are each independently selected from the group of hydrogen, halogen, -CN, $-CF_3$, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylcyano, -(C_1-C_6)alkylheteroaryl, -(C_1-C_6)alkylaryl, aryl, heteroaryl, heterocycle, -(C_0-C_6)alkyl-OR^5, -O-(C_2-C_6)alkyl-OR^5, -NR^5(C_2-C_6)alkyl-OR^6, -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -O-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -NR^5-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo-OR^5, -(C_1-C_6)alkylhalo-NR^5R^6, -(C_0-C_6)alkyl-S-R^5, -O-(C_2-C_6)alkyl-S-R^5, -NR^5-(C_2-C_6)alkyl-S-R^6, -(C_0-C_6)alkyl-S(=O)-R^5, -O-(C_1-C_6)alkyl-S(=O)-R^5, -NR^5-(C_1-C_6)alkyl-S(=O)-R^6, -(C_0-C_6)alkyl-$S(=O)_2$-R^5, -O-(C_1-C_6)alkyl-$S(=O)_2$-R^5, -NR^5-(C_1-C_6)alkyl-$S(=O)_2$-R^6, -(C_0-C_6)alkyl-NR^5R^6, -O-(C_2-C_6)alkyl-NR^5R^6, -NR^5-(C_2-C_6)alkyl-NR^6R^7, -(C_0-C_6)alkyl-$S(=O)_2NR^5R^6$, -O-(C_1-C_6)alkyl-$S(=O)_2NR^5R^6$, -NR^5-(C_1-C_6)alkyl-$S(=O)_2NR^6R^7$, -(C_0-C_6)alkyl-NR^5-$S(=O)_2R^6$, -O-(C_2-C_6)alkyl-NR^5-$S(=O)_2R^6$, -NR^5-(C_2-C_6)alkyl-NR^6-$S(=O)_2R^7$, -(C_0-C_6)alkyl-C(=O)-NR^5R^6, -O-(C_1-C_6)alkyl-C(=O)-NR^5R^6, -NR^5-(C_1-C_6)alkyl-C(=O)-NR^6R^7, -(C_0-C_6)alkyl-NR^5C(=O)-R^6, -O-(C_2-C_6)alkyl-NR^5C(=O)-R^6, -NR^5-(C_2-C_6)alkyl-NR^6C(=O)-R^7, -O-(C_2-C_6)alkyl-OC(=O)-R^5, -NR^5-(C_2-C_6)alkyl-OC(=O)-R^6, -(C_0-C_6)alkyl-C(=O)-OR^5, -O-(C_1-C_6)alkyl-C(=O)-OR^5, -NR^5-(C_1-C_6)alkyl-C(=O)-OR^6, -(C_0-C_6)alkyl-C(=O)-R^5, -O-(C_1-C_6)alkyl-C(=O)-R^5, -NR^5-(C_1-C_6)alkyl-C(=O)-R^6, -(C_0-C_6)alkyl-NR^5-C(=O)-OR^6, -(C_0-C_6)alkyl-NR^5-C(=O)-NR^6R^7, -O-(C_2-C_6)alkyl-NR^5-C(=O)-NR^6R^7 and -NR^5-(C_2-C_6)alkyl-NR^6-C(=O)-NR^7R^8;

R^5, R^6, R^7 and R^8 are each independently hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)alkylcyano, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl;

Any two radicals of R (R^5, R^6, R^7 or R^8) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

M^1 is selected from an optionally substituted 3 to 10 membered ring selected from the group of aryl, heteroaryl, heterocyclic and cycloalkyl;

M^2 is selected from the group of a hydrogen or an optionally substituted radical selected from the group of -(C_0-C_6)alkyl-R^9, -(C_1-C_6)alkylhalo, -(C_2-C_6)alkyl-NR^9R^{10}, -(C_2-C_6)alkyl-OR^9, -(C_2-C_6)alkyl-SR^9, -(C_0-C_6)alkyl-C(=O)-R^9, -(C_2-C_6)alkyl-S(O)-R^9, -(C_0-C_6)alkyl-C(=O)NR^9R^{10} and -(C_0-C_6)alkyl-$S(O)_2$-R^9;

R^9 and R^{10} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)alkylcyano, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl;

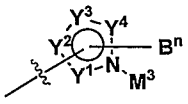
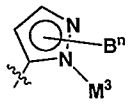
M^3 is an optionally substituted radical selected from the group of -(C_0-C_6)alkyl-R^{11}, -(C_1-C_6)alkylhalo, -(C_2-C_6)alkyl-$NR^{11}R^{12}$, -(C_2-C_6)alkyl-OR^{11} and -(C_2-C_6)alkyl-SR^{11}; and

R^{11} and R^{12} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)alkylcyano, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl;

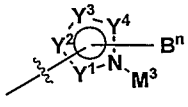
provided that according to proviso (i):

when M^3 is -(C_0)-R^{11} (that is when M^3 is -R^{11}), then R^{11} is not H;

and provided that according to proviso (ii):

 can not be  ;

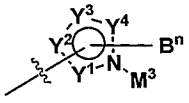
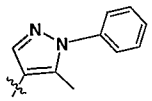
and provided that according to proviso (iii):

when M^1 is aryl, M^2 is H, X^1 is C, X^2 is C, X^3 is C, X^4 is N, then  is not linked to X^2;

and provided that according to proviso (iv):

A^1 and A^2 radicals are not linked to form an imidazopyridazinyl ring;

and provided that according to proviso (v):

when  is  and linked to X^4, X^1 is C, X^2 is S, X^3 is C, X^4 is C, n is 1, A^1 is H, Y^1, Y^2, Y^3 are C, Y^4 is N, then M^1 can not be an optionally substituted aryl, 1-methyl-1H-indazol-4-yl, 1H-indazol-3-yl and 1H-indazol-4-yl;

and provided that according to proviso (vi):

when M^3 is 4-methylphenyl, then B^n can not be a phenyl;

and provided that according to proviso (vii):

when M^1M^2N is linked to X^1, and X^1 is C, X^2 is S, X^3 is C, X^4 is C, to provide a thiazole ring, n is 1, then A^1 is not a pyridyl;

and provided that according to proviso (viii):

when M^1M^2N is linked to X^1, and X^1 is C, X^2 is S, X^3 is C, X^4 is C, to provide a thiazole ring, n is 1, then A^1 is not an optionally substituted imidazolyl or triazolyl ring.

The compounds N-phenyl-4-(1H-pyrazol-3-yl)-2-thiazolamine hydrobromide (1:1) [358779-21-2], 4-(1H-indazol-3-yl)-N-(4-methoxyphenyl)-2-thiazolamine hydrobromide (1:1) [358779-27-8], 4-(1H-indazol-3-yl)-N-phenyl-2-thiazolamine

hydrobromide (1:1) [358779-28-9] known as such from international patent publication WO2001/64674 are excluded from the present invention by virtue of proviso (i);

The compounds 4-(2-(4-(octyloxy)-3-(trifluoromethyl)phenylamino)thiazol-4-yl)-1*H*-pyrazole-3-carbonitrile [914668-55-6] known as such from International patent publication WO2006/122011 are excluded from the present invention by virtue of proviso (i);

The compounds 2-amino-N-[[3-[5-[5-(phenylamino)-1,3,4-oxadiazol-2-yl]-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]methyl]-(2S)-propanamide [895524-13-7], 2-amino-N-[[3-[5-[5-[(2-methoxyphenyl)amino]-1,3,4-oxadiazol-2-yl]-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]methyl]-(2S)-propanamide [895524-14-8], 2-amino-N-[[3-[5-[5-[(2-methoxy-5-methylphenyl)amino]-1,3,4-oxadiazol-2-yl]-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]methyl]-(2S)-propanamide [895524-15-9], 2-amino-N-[[3-[5-[5-[(2,4-dimethoxyphenyl)amino]-1,3,4-oxadiazol-2-yl]-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]methyl]-(2S)-propanamide [895524-16-0], 2-amino-N-[[3-[5-[5-[(2,5-dimethoxyphenyl)amino]-1,3,4-oxadiazol-2-yl]-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]methyl]-(2S)-propanamide [895524-17-1], 2-amino-N-[[3-[5-[5-[(5-chloro-2-methoxyphenyl)amino]-1,3,4-oxadiazol-2-yl]-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]methyl]-(2S)-propanamide [895524-18-2], 2-amino-N-[[3-[5-[5-[[2-(difluoromethoxy)phenyl]amino]-1,3,4-oxadiazol-2-yl]-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]methyl]-(2S)-propanamide [895524-19-3], 2-amino-N-[[3-[5-[5-[[2-(trifluoromethoxy)phenyl]amino]-1,3,4-oxadiazol-2-yl]-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]methyl]-(2S)-propanamide [895524-20-6], 2-amino-N-[[3-[5-[5-[(4-methoxy[1,1'-biphenyl]-3-yl)amino]-1,3,4-oxadiazol-2-yl]-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]methyl]-(2S)-propanamide [895524-21-7], 2-amino-N-[[3-[5-[5-[(2-methoxy-5-nitrophenyl)amino]-1,3,4-oxadiazol-2-yl]-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]methyl]-(2S)-propanamide [895524-22-8], 2-amino-N-[[3-[5-[5-(7-benzothiazolylamino)-1,3,4-oxadiazol-2-yl]-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]methyl]-(2S)-propanamide [895524-23-9], [(1S)-1-methyl-2-oxo-2-[[[3-[5-[5-(phenylamino)-1,3,4-oxadiazol-2-yl]-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]methyl]amino]ethyl]-, 1,1-dimethylethyl ester carbamic acid [895524-52-

4P] known as such from international patent publication WO2006/069155 are excluded from the present invention by virtue of proviso (ii);

The compound 5-methoxy-2-([1-(2-methoxyphenyl)-1',3-dimethyl-1H,1'H-4,4'-bipyrazol-5-yl]amino)benzoic acid [870188-47-9] known as such from international patent publication WO2005/112923 is excluded from the present invention by virtue of proviso (iii).

The compounds (Z)-5-(3-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyrazin-2-ylamino)-2,3-dihydro-1H-inden-1-one oxime [915705-05-4] known as such from international patent publication WO2005/125101 is excluded from the present invention by virtue of proviso (iv);

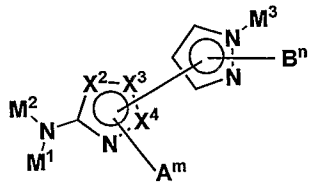
The compounds N-(4-methylphenyl)-4-(5-methyl-1-phenyl-1H-pyrazol-4-yl) 2-Thiazolamine [209117-29-3], N-(4-methoxyphenyl)-4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-2-thiazolamine [209117-30-6], 4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-N-phenyl-2-thiazolamine [209117-27-1], N-(4-chlorophenyl)-4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-2-thiazolamine [209117-32-8], known as such from Singh, S.P. et al. (1997) J: Indian Chem. Soc. (74, 11-12):940-942, are excluded from the present invention by virtue of proviso (v);

The compounds 4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-N-(3-(methylthio)phenyl)thiazol-2-amine, N^1-isopropyl-N^4-(4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)thiazol-2-yl)-N^1-phenylbenzene-1,4-diamine, N^4,N^4-diethyl-2-methyl-N^1-(4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)thiazol-2-yl)benzene-1,4-diamine; N-(1H-indazol-4-yl)-4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)thiazol-2-amine; N-(2,4-dimethoxyphenyl)-4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)thiazol-2-amine; 4-(4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)thiazol-2-ylamino)phenol; 4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-N-(4-phenoxyphenyl)thiazol-2-amine; 4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-N-(1-methyl-1H-indazol-4-yl)thiazol-2-amine; N-(1H-indazol-3-yl)-4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)thiazol-2-amine; N-(3,5-dimethylphenyl)-4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)thiazol-2-amine; 4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-N-(naphthalen-1-yl)thiazol-2-amine; 4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-N-(2,4,5-trimethylphenyl)thiazol-2-amine; 4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-N-(3-

(trifluoromethyl)phenyl)thiazol-2-amine; N-(3-bromophenyl)-4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)thiazol-2-amine; 3-(4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)thiazol-2-ylamino)benzoyl chloride; 4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-N-*m*-tolylthiazol-2-amine; N-(3-fluorophenyl)-4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)thiazol-2-amine; N-(2-methoxyphenyl)-4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)thiazol-2-amine, known as such from US patent publication US7244739 are excluded from the present invention by virtue of proviso (v).

The compounds are 3-[5-[(4-chlorophenyl)azo]-2-(phenylamino)-4-thiazolyl]-1-(4-methylphenyl)-5-phenyl-1H-pyrazole-4-carbonitrile [198840-15-2], 1-(4-methylphenyl)-3-[5-[(4-methylphenyl)azo]-2-(phenylamino)-4-thiazolyl]-5-phenyl-1H-pyrazole-4-carbonitrile [198840-14-1], 1-(4-methylphenyl)-5-phenyl-3-[2-(phenylamino)-5-(phenylazo)-4-thiazolyl]-1H-pyrazole-4-carbonitrile [198840-13-0], 1-(4-methylphenyl)-5-phenyl-3-[2-(phenylamino)-4-thiazolyl]-1H-pyrazole-4-carbonitrile [198840-12-9], known as such from Hassan, N.M. et al (1997) J. Chem. Res., Syn. (10): 350-351, are excluded from the present invention by virtue of proviso (vi).

In a preferred aspect of Formula (I), the invention provides a compound according to Formula (II),



(II)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof, wherein:

X^2, X^3 and X^4 are each independently selected from the group of C, N, O, S and C=C representing a 5 or 6 membered heteroaryl ring which may further be substituted by 1 to 3 radicals A^m;

m is an integer ranging from 1 to 3;

A^m radicals are each independently selected from the group of hydrogen, halogen, -CN, $-CF_3$, and an optionally substituted radical selected from the group of $-(C_1-C_6)$alkyl, $-(C_1-C_6)$alkylhalo, $-(C_3-C_7)$cycloalkyl, $-(C_1-C_6)$alkylcyano, $-(C_1-C_6)$alkylheteroaryl, $-(C_1-C_6)$alkylaryl, aryl, heteroaryl, heterocycle, $-(C_0-C_6)$alkyl-OR^1, $-NR^1(C_2-C_6)$alkyl-OR^2, $-(C_3-C_7)$cycloalkyl-(C_1-C_6)alkyl, $-O-(C_3-C_7)$cycloalkyl-(C_1-C_6)alkyl, $-NR^1-(C_3-C_7)$cycloalkyl-(C_1-C_6)alkyl, $-(C_1-C_6)$alkylhalo-OR^1, $-(C_1-C_6)$alkylhalo-NR^1R^2, $-NR^1-(C_2-C_6)$alkyl-S-R^2, $-(C_0-C_6)$alkyl-S(=O)-R^1, $-NR^1-(C_1-C_6)$alkyl-S(=O)-R^2, $-(C_0-C_6)$alkyl-$S(=O)_2-R^1$, $-NR^1-(C_1-C_6)$alkyl-$S(=O)_2-R^2$, $-(C_0-C_6)$alkyl-NR^1R^2, $-NR^1-(C_2-C_6)$alkyl-NR^2R^3, $-(C_0-C_6)$alkyl-$S(=O)_2NR^1R^2$, $-NR^1-(C_1-C_6)$alkyl-$S(=O)_2NR^2R^3$, $-(C_0-C_6)$alkyl-$NR^1-S(=O)_2R^2$, $-NR^1-(C_2-C_6)$alkyl-$NR^2-S(=O)_2R^3$, $-(C_0-C_6)$alkyl-C(=O)-NR^1R^2, $-NR^1-(C_1-C_6)$alkyl-C(=O)-NR^2R^3, $-(C_0-C_6)$alkyl-$NR^1C(=O)-R^2$, $-NR^1-(C_2-C_6)$alkyl-$NR^2C(=O)-R^3$, $-NR^1-(C_2-C_6)$alkyl-$OC(=O)-R^2$, $-(C_0-C_6)$alkyl-C(=O)-OR^1, $-NR^1-(C_1-C_6)$alkyl-C(=O)-OR^2, $-(C_0-C_6)$alkyl-C(=O)-R^1, $-NR^1-(C_1-C_6)$alkyl-C(=O)-R^2, $-(C_0-C_6)$alkyl-NR^1-C(=O)-OR^2, $-(C_0-C_6)$alkyl-NR^1-C(=O)-NR^2R^3, and $-NR^1-(C_2-C_6)$alkyl-NR^2-C(=O)-NR^3R^4;

Any two radicals of A^m (A^1 and A^2) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

R^1, R^2, R^3 and R^4 are each independently hydrogen or an optionally substituted radical selected from the group of $-(C_1-C_6)$alkylhalo, $-(C_1-C_6)$alkyl, $-(C_1-C_6)$alkylcyano, $-(C_3-C_7)$cycloalkyl, $-(C_4-C_{10})$alkylcycloalkyl, heteroaryl, $-(C_1-C_6)$alkylheteroaryl, aryl, heterocycle and $-(C_1-C_6)$alkylaryl;

Any two radicals of R (R^1, R^2, R^3 or R^4) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

n is an integer ranging from 1 to 2;

B^n radicals are each independently selected from the group of hydrogen, halogen, -CN, $-CF_3$, and an optionally substituted radical selected from the group of $-(C_1-C_6)$alkyl, -

(C_1-C_6)alkylhalo, -(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylcyano, -(C_1-C_6)alkylheteroaryl, -(C_1-C_6)alkylaryl, aryl, heteroaryl, heterocycle, -(C_0-C_6)alkyl-OR^5, -O-(C_2-C_6)alkyl-OR^5, -NR^5(C_2-C_6)alkyl-OR^6, -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -O-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -NR^5-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo-OR^5, -(C_1-C_6)alkylhalo-NR^5R^6, -(C_0-C_6)alkyl-S-R^5, -O-(C_2-C_6)alkyl-S-R^5, -NR^5-(C_2-C_6)alkyl-S-R^6, -(C_0-C_6)alkyl-S(=O)-R^5, -O-(C_1-C_6)alkyl-S(=O)-R^5, -NR^5-(C_1-C_6)alkyl-S(=O)-R^6, -(C_0-C_6)alkyl-S(=O)$_2$-R^5, -O-(C_1-C_6)alkyl-S(=O)$_2$-R^5, -NR^5-(C_1-C_6)alkyl-S(=O)$_2$-R^6, -(C_0-C_6)alkyl-NR^5R^6, -O-(C_2-C_6)alkyl-NR^5R^6, -NR^5-(C_2-C_6)alkyl-NR^6R^7, -(C_0-C_6)alkyl-S(=O)$_2$$NR^5R^6$, -O-($C_1$-$C_6$)alkyl-S(=O)$_2$$NR^5R^6$, -$NR^5$-($C_1$-$C_6$)alkyl-S(=O)$_2$$NR^6R^7$, -($C_0$-$C_6$)alkyl-$NR^5$-S(=O)$_2$$R^6$, -O-($C_2$-$C_6$)alkyl-$NR^5$-S(=O)$_2$$R^6$, -$NR^5$-($C_2$-$C_6$)alkyl-$NR^6$-S(=O)$_2$$R^7$, -($C_0$-$C_6$)alkyl-C(=O)-$NR^5R^6$, -O-($C_1$-$C_6$)alkyl-C(=O)-$NR^5R^6$, -$NR^5$-($C_1$-$C_6$)alkyl-C(=O)-$NR^6R^7$, -($C_0$-$C_6$)alkyl-$NR^5$C(=O)-$R^6$, -O-($C_2$-$C_6$)alkyl-$NR^5$C(=O)-$R^6$, -$NR^5$-($C_2$-$C_6$)alkyl-$NR^6$C(=O)-$R^7$, -O-($C_2$-$C_6$)alkyl-OC(=O)-$R^5$, -$NR^5$-($C_2$-$C_6$)alkyl-OC(=O)-$R^6$, -($C_0$-$C_6$)alkyl-C(=O)-$OR^5$, -O-($C_1$-$C_6$)alkyl-C(=O)-$OR^5$, -$NR^5$-($C_1$-$C_6$)alkyl-C(=O)-$OR^6$, -($C_0$-$C_6$)alkyl-C(=O)-$R^5$, -O-($C_1$-$C_6$)alkyl-C(=O)-$R^5$, -$NR^5$-($C_1$-$C_6$)alkyl-C(=O)-$R^6$, -($C_0$-$C_6$)alkyl-$NR^5$-C(=O)-$OR^6$, -($C_0$-$C_6$)alkyl-$NR^5$-C(=O)-$NR^6R^7$, -O-($C_2$-$C_6$)alkyl-$NR^5$-C(=O)-$NR^6R^7$ and -NR^5-(C_2-C_6)alkyl-NR^6-C(=O)-NR^7R^8;

R^5, R^6, R^7 and R^8 are each independently hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)alkylcyano, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl;

Any two radicals of R (R^5, R^6, R^7 or R^8) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

M^1 is selected from an optionally substituted 3 to 10 membered ring selected from the group of aryl, heteroaryl, heterocyclic and cycloalkyl;

M^2 is selected from the group of a hydrogen or an optionally substituted radical selected from the group of -(C_0-C_6)alkyl-R^9, -(C_1-C_6)alkylhalo, -(C_2-C_6)alkyl-NR^9R^{10}, -(C_2-C_6)alkyl-OR^9, -(C_2-C_6)alkyl-SR^9, -(C_0-C_6)alkyl-C(=O)-R^9, -(C_2-C_6)alkyl-S(O)-R^9, -(C_0-C_6)alkyl-C(=O)NR^9R^{10} and -(C_0-C_6)alkyl-$S(O)_2$-R^9;

R^9 and R^{10} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)alkylcyano, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl;

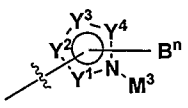
M^3 is an optionally substituted radical selected from the group of -(C_3-C_7)cycloalkyl, aryl, heteroaryl, heterocycle, -(C_1-C_6)alkyl-R^{11}, -(C_1-C_6)alkylhalo, -(C_2-C_6)alkyl-$NR^{11}R^{12}$, -(C_2-C_6)alkyl-OR^{11} and -(C_2-C_6)alkyl-SR^{11}; and

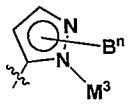
R^{11} and R^{12} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)alkylcyano, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl;

provided that according to proviso (i):

when M^3 is -(C_0)-R^{11} (that is when M^3 is -R^{11}), then R^{11} is not H;

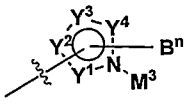
and provided that according to proviso (ii):



can not be


;

and provided that according to proviso (iii):

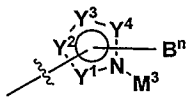
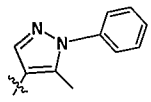
when M^1 is aryl, M^2 is H, X^2 is C, X^3 is C, X^4 is N, then


is not linked to X^2;

and provided that according to proviso (iv):

A^1 and A^2 radicals are not linked to form an imidazopyridazinyl ring;

and provided that according to proviso (v):

when  is  and linked to X^4, X^2 is S, X^3 is C, X^4 is C, n is 1, A^1 is H, then M^1 can not be an optionally substituted aryl, 1-methyl-1H-indazol-4-yl, 1H-indazol-3-yl and 1H-indazol-4-yl;

and provided that according to proviso (vi):

when M^3 is 4-methylphenyl, then B^n can not be a phenyl;

and provided that according to proviso (vii):

when X^2 is S, X^3 is C, X^4 is C, n is 1, then A^1 when linked to either X^3 or X^4 is not a pyridyl;

and provided that according to proviso (viii):

when X^2 is S, X^3 is C, X^4 is C, to provide a thiazole ring, n is 1, then A^1 is not an optionally substituted imidazolyl or triazolyl ring.

In a specific aspect of Formula (II), the invention provides a compound wherein:

X^2 is a nitrogen, an oxygen, or a sulfur atom, X^3 is a carbon atom or a nitrogen atom, X^4 is a carbon or a nitrogen atom, representing a 5 membered heteroaryl, which may further be substituted by 1 to 2 radicals A^m;

m is an integer ranging from 1 to 2;

A^m radicals are each independently selected from the group of hydrogen, halogen, -CN, $-CF_3$, and an optionally substituted radical selected from the group of $-(C_1-C_6)$alkyl, $-(C_1-C_6)$alkylhalo, $-(C_3-C_7)$cycloalkyl, $-(C_1-C_6)$alkylcyano, $-(C_1-C_6)$alkylheteroaryl, $-(C_1-C_6)$alkylaryl, aryl, heteroaryl, heterocycle, $-(C_0-C_6)$alkyl-OR^1, $-NR^1(C_2-C_6)$alkyl-OR^2, $-(C_3-C_7)$cycloalkyl-(C_1-C_6)alkyl, -O-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, $-NR^1-(C_3-C_7)$cycloalkyl-(C_1-C_6)alkyl, $-(C_1-C_6)$alkylhalo-OR^1, $-(C_1-C_6)$alkylhalo-NR^1R^2, $-NR^1-$

$(C_2\text{-}C_6)$alkyl-S-R^2, -$(C_0\text{-}C_6)$alkyl-S(=O)-R^1, -NR^1-$(C_1\text{-}C_6)$alkyl-S(=O)-R^2, -$(C_0\text{-}C_6)$alkyl-S(=O)$_2$-R^1, -NR^1-$(C_1\text{-}C_6)$alkyl-S(=O)$_2$-R^2, -$(C_0\text{-}C_6)$alkyl-NR^1R^2, -NR^1-$(C_2\text{-}C_6)$alkyl-NR^2R^3, -$(C_0\text{-}C_6)$alkyl-S(=O)$_2NR^1R^2$, -NR^1-$(C_1\text{-}C_6)$alkyl-S(=O)$_2NR^2R^3$, -$(C_0\text{-}C_6)$alkyl-NR^1-S(=O)$_2R^2$, -NR^1-$(C_2\text{-}C_6)$alkyl-NR^2-S(=O)$_2R^3$, -$(C_0\text{-}C_6)$alkyl-C(=O)-NR^1R^2, -NR^1-$(C_1\text{-}C_6)$alkyl-C(=O)-NR^2R^3, -$(C_0\text{-}C_6)$alkyl-NR^1C(=O)-R^2, -NR^1-$(C_2\text{-}C_6)$alkyl-NR^2C(=O)-R^3, -NR^1-$(C_2\text{-}C_6)$alkyl-OC(=O)-R^2, -$(C_0\text{-}C_6)$alkyl-C(=O)-OR^1, -NR^1-$(C_1\text{-}C_6)$alkyl-C(=O)-OR^2, -$(C_0\text{-}C_6)$alkyl-C(=O)-R^1, -NR^1-$(C_1\text{-}C_6)$alkyl-C(=O)-R^2, -$(C_0\text{-}C_6)$alkyl-NR^1-C(=O)-OR^2, -$(C_0\text{-}C_6)$alkyl-NR^1-C(=O)-NR^2R^3, and -NR^1-$(C_2\text{-}C_6)$alkyl-NR^2-C(=O)-NR^3R^4;

Any two radicals of A^m (A^1 and A^2) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

R^1, R^2, R^3 and R^4 are each independently hydrogen or an optionally substituted radical selected from the group of -$(C_1\text{-}C_6)$alkylhalo, -$(C_1\text{-}C_6)$alkyl, -$(C_1\text{-}C_6)$alkylcyano, -$(C_3\text{-}C_7)$cycloalkyl, -$(C_4\text{-}C_{10})$alkylcycloalkyl, heteroaryl, -$(C_1\text{-}C_6)$alkylheteroaryl, aryl, heterocycle and -$(C_1\text{-}C_6)$alkylaryl;

Any two radicals of R (R^1, R^2, R^3 or R^4) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

n is an integer ranging from 1 to 2;

B^n radicals are each independently selected from the group of hydrogen, halogen, -CN, -CF_3, and an optionally substituted radical selected from the group of -$(C_1\text{-}C_6)$alkyl, -$(C_1\text{-}C_6)$alkylhalo, -$(C_3\text{-}C_7)$cycloalkyl, -$(C_1\text{-}C_6)$alkylcyano, -$(C_1\text{-}C_6)$alkylheteroaryl, -$(C_1\text{-}C_6)$alkylaryl, aryl, heteroaryl, heterocycle, -$(C_0\text{-}C_6)$alkyl-OR^5, -O-$(C_2\text{-}C_6)$alkyl-OR^5, -$NR^5$$(C_2\text{-}C_6)$alkyl-$OR^6$, -$(C_3\text{-}C_7)$cycloalkyl-$(C_1\text{-}C_6)$alkyl, -O-$(C_3\text{-}C_7)$cycloalkyl-$(C_1\text{-}C_6)$alkyl, -$NR^5$-$(C_3\text{-}C_7)$cycloalkyl-$(C_1\text{-}C_6)$alkyl, -$(C_1\text{-}C_6)$alkylhalo-$OR^5$, -$(C_1\text{-}C_6)$alkylhalo-$NR^5R^6$, -$(C_0\text{-}C_6)$alkyl-S-$R^5$, -O-$(C_2\text{-}C_6)$alkyl-S-$R^5$, -$NR^5$-$(C_2\text{-}C_6)$alkyl-S-$R^6$, -$(C_0\text{-}C_6)$alkyl-S(=O)-$R^5$, -O-$(C_1\text{-}C_6)$alkyl-S(=O)-$R^5$, -$NR^5$-$(C_1\text{-}C_6)$alkyl-S(=O)-$R^6$, -$(C_0\text{-}C_6)$alkyl-S(=O)$_2$-$R^5$, -O-$(C_1\text{-}C_6)$alkyl-S(=O)$_2$-$R^5$, -$NR^5$-$(C_1\text{-}C_6)$alkyl-S(=O)$_2$-$R^6$, -

$(C_0\text{-}C_6)$alkyl-NR^5R^6, -O-$(C_2\text{-}C_6)$alkyl-NR^5R^6, -NR^5-$(C_2\text{-}C_6)$alkyl-NR^6R^7, -$(C_0\text{-}C_6)$alkyl-$S(=O)_2NR^5R^6$, -O-$(C_1\text{-}C_6)$alkyl-$S(=O)_2NR^5R^6$, -NR^5-$(C_1\text{-}C_6)$alkyl-$S(=O)_2NR^6R^7$, -$(C_0\text{-}C_6)$alkyl-NR^5-$S(=O)_2R^6$, -O-$(C_2\text{-}C_6)$alkyl-NR^5-$S(=O)_2R^6$, -NR^5-$(C_2\text{-}C_6)$alkyl-NR^6-$S(=O)_2R^7$, -$(C_0\text{-}C_6)$alkyl-C(=O)-NR^5R^6, -O-$(C_1\text{-}C_6)$alkyl-C(=O)-NR^5R^6, -NR^5-$(C_1\text{-}C_6)$alkyl-C(=O)-NR^6R^7, -$(C_0\text{-}C_6)$alkyl-NR^5C(=O)-R^6, -O-$(C_2\text{-}C_6)$alkyl-NR^5C(=O)-R^6, -NR^5-$(C_2\text{-}C_6)$alkyl-NR^6C(=O)-R^7, -O-$(C_2\text{-}C_6)$alkyl-OC(=O)-R^5, -NR^5-$(C_2\text{-}C_6)$alkyl-OC(=O)-R^6, -$(C_0\text{-}C_6)$alkyl-C(=O)-OR^5, -O-$(C_1\text{-}C_6)$alkyl-C(=O)-OR^5, -NR^5-$(C_1\text{-}C_6)$alkyl-C(=O)-OR^6, -$(C_0\text{-}C_6)$alkyl-C(=O)-R^5, -O-$(C_1\text{-}C_6)$alkyl-C(=O)-R^5, -NR^5-$(C_1\text{-}C_6)$alkyl-C(=O)-R^6, -$(C_0\text{-}C_6)$alkyl-NR^5-C(=O)-OR^6, -$(C_0\text{-}C_6)$alkyl-NR^5-C(=O)-NR^6R^7, -O-$(C_2\text{-}C_6)$alkyl-NR^5-C(=O)-NR^6R^7 and -NR^5-$(C_2\text{-}C_6)$alkyl-NR^6-C(=O)-NR^7R^8;

R^5, R^6, R^7 and R^8 each independently hydrogen or an optionally substituted radical selected from the group of -$(C_1\text{-}C_6)$alkylhalo, -$(C_1\text{-}C_6)$alkyl, -$(C_3\text{-}C_7)$cycloalkyl, -$(C_4\text{-}C_{10})$alkylcycloalkyl and heterocycle;

Any two radicals of of R (R^5, R^6, R^7 or R^8) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

M^1 is selected from an optionally substituted aryl and heteroaryl;

M^2 is a hydrogen or an optionally substituted -$(C_1\text{-}C_6)$alkyl-R^9;

R^9 is a hydrogen;

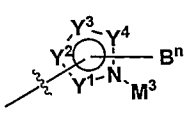
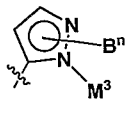
M^3 is an optionally substituted radical selected from the group of -$(C_3\text{-}C_7)$cycloalkyl, aryl, heteroaryl, heterocycle, -$(C_1\text{-}C_6)$alkyl-R^{11}, -$(C_1\text{-}C_6)$alkylhalo, -$(C_2\text{-}C_6)$alkyl-$NR^{11}R^{12}$, -$(C_2\text{-}C_6)$alkyl-OR^{11} and -$(C_2\text{-}C_6)$alkyl-SR^{11}; and

R^{11} and R^{12} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of -$(C_1\text{-}C_6)$alkylhalo, -$(C_1\text{-}C_6)$alkyl, -$(C_1\text{-}C_6)$alkylcyano, -$(C_3\text{-}C_7)$cycloalkyl, -$(C_4\text{-}C_{10})$alkylcycloalkyl, heteroaryl, -$(C_1\text{-}C_6)$alkylheteroaryl, aryl, heterocycle and -$(C_1\text{-}C_6)$alkylaryl;

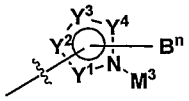
provided that according to proviso (i):

when M^3 is -(C_0)-R^{11} (that is when M^3 is -R^{11}), then R^{11} is not H;

and provided that according to proviso (ii):

 can not be  ;

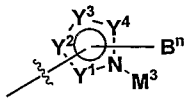
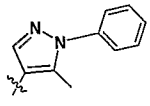
and provided that according to proviso (iii):

when M^1 is aryl, X^2 is C, X^3 is C, X^4 is N, then  is not linked to X^2;

and provided that according to proviso (iv):

A^1 and A^2 radicals are not linked to form an imidazopyridazinyl ring;

and provided that according to proviso (v):

when  is  and linked to X^4, X^2 is S, X^3 is C, X^4 is C, n is 1, A^1 is H, then M^1 can not be an optionally substituted aryl, 1-methyl-1H-indazol-4-yl, 1H-indazol-3-yl and 1H-indazol-4-yl;

and provided that according to proviso (vi):

when M^3 is 4-methylphenyl, then B^n can not be a phenyl;

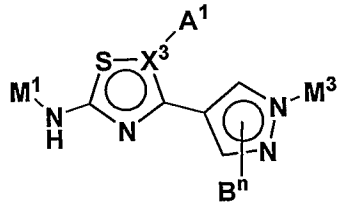
and provided that according to proviso (vii):

when X^2 is S, X^3 is C, X^4 is C, n is 1, then A^1 when linked to either X^3 or X^4 is not a pyridyl;

and provided that according to proviso (viii):

when X^2 is S, X^3 is C, X^4 is C, to provide a thiazole ring, n is 1, then A^1 is not an optionally substituted imidazolyl or triazolyl ring.

In a more preferred aspect of Formula (II), the invention provides a compound according to Formula (III),



(III)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof, wherein:

X^3 is selected from C or N which may further be substituted by A^1;

A^1 radicals are each independently selected from the group of hydrogen, halogen, -CN, $-CF_3$, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylcyano, -(C_1-C_6)alkylheteroaryl, -(C_1-C_6)alkylaryl, heterocycle, -(C_0-C_6)alkyl-OR^1, -NR^1(C_2-C_6)alkyl-OR^2, -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -O-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -NR^1-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo-OR^1, -(C_1-C_6)alkylhalo-NR^1R^2, -NR^1-(C_2-C_6)alkyl-S-R^2, -(C_0-C_6)alkyl-S(=O)-R^1, -NR^1-(C_1-C_6)alkyl-S(=O)-R^2, -(C_0-C_6)alkyl-S(=O)$_2$-R^1, -NR^1-(C_1-C_6)alkyl-S(=O)$_2$-R^2, -(C_0-C_6)alkyl-NR^1R^2, -NR^1-(C_2-C_6)alkyl-NR^2R^3, -(C_0-C_6)alkyl-S(=O)$_2$$NR^1R^2$, -$NR^1$-($C_1$-$C_6$)alkyl-S(=O)$_2$$NR^2R^3$, -($C_0$-$C_6$)alkyl-$NR^1$-S(=O)$_2$$R^2$, -$NR^1$-($C_2$-$C_6$)alkyl-$NR^2$-S(=O)$_2$$R^3$, -($C_0$-$C_6$)alkyl-C(=O)-$NR^1R^2$, -$NR^1$-($C_1$-$C_6$)alkyl-C(=O)-$NR^2R^3$, -($C_0$-$C_6$)alkyl-$NR^1$C(=O)-$R^2$, -$NR^1$-($C_2$-$C_6$)alkyl-$NR^2$C(=O)-$R^3$, -$NR^1$-($C_2$-$C_6$)alkyl-OC(=O)-$R^2$, -($C_0$-$C_6$)alkyl-C(=O)-$OR^1$, -$NR^1$-($C_1$-$C_6$)alkyl-C(=O)-$OR^2$, -($C_0$-$C_6$)alkyl-C(=O)-$R^1$, -$NR^1$-($C_1$-$C_6$)alkyl-C(=O)-$R^2$, -($C_0$-$C_6$)alkyl-$NR^1$-C(=O)-$OR^2$, -($C_0$-$C_6$)alkyl-$NR^1$-C(=O)-$NR^2R^3$, and -$NR^1$-($C_2$-$C_6$)alkyl-$NR^2$-C(=O)-$NR^3R^4$;

R^1, R^2, R^3 and R^4 are each independently hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)alkylcyano, -(C_3-

C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl;

Any two radicals of R (R^1, R^2, R^3 or R^4) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

n is an integer ranging from 1 to 2;

B^n radicals are each independently selected from the group of hydrogen, halogen, -CN, -CF_3, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylcyano, -(C_1-C_6)alkylheteroaryl, -(C_1-C_6)alkylaryl, aryl, heteroaryl, heterocycle, -(C_0-C_6)alkyl-OR^5, -O-(C_2-C_6)alkyl-OR^5, -NR^5(C_2-C_6)alkyl-OR^6, -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -O-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -NR^5-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo-OR^5, -(C_1-C_6)alkylhalo-NR^5R^6, -(C_0-C_6)alkyl-S-R^5, -O-(C_2-C_6)alkyl-S-R^5, -NR^5-(C_2-C_6)alkyl-S-R^6, -(C_0-C_6)alkyl-S(=O)-R^5, -O-(C_1-C_6)alkyl-S(=O)-R^5, -NR^5-(C_1-C_6)alkyl-S(=O)-R^6, -(C_0-C_6)alkyl-$S(=O)_2$-R^5, -O-(C_1-C_6)alkyl-$S(=O)_2$-R^5, -NR^5-(C_1-C_6)alkyl-$S(=O)_2$-R^6, -(C_0-C_6)alkyl-NR^5R^6, -O-(C_2-C_6)alkyl-NR^5R^6, -NR^5-(C_2-C_6)alkyl-NR^6R^7, -(C_0-C_6)alkyl-$S(=O)_2NR^5R^6$, -O-(C_1-C_6)alkyl-$S(=O)_2NR^5R^6$, -NR^5-(C_1-C_6)alkyl-$S(=O)_2NR^6R^7$, -(C_0-C_6)alkyl-NR^5-$S(=O)_2R^6$, -O-(C_2-C_6)alkyl-NR^5-$S(=O)_2R^6$, -NR^5-(C_2-C_6)alkyl-NR^6-$S(=O)_2R^7$, -(C_0-C_6)alkyl-C(=O)-NR^5R^6, -O-(C_1-C_6)alkyl-C(=O)-NR^5R^6, -NR^5-(C_1-C_6)alkyl-C(=O)-NR^6R^7, -(C_0-C_6)alkyl-NR^5C(=O)-R^6, -O-(C_2-C_6)alkyl-NR^5C(=O)-R^6, -NR^5-(C_2-C_6)alkyl-NR^6C(=O)-R^7, -O-(C_2-C_6)alkyl-OC(=O)-R^5, -NR^5-(C_2-C_6)alkyl-OC(=O)-R^6, -(C_0-C_6)alkyl-C(=O)-OR^5, -O-(C_1-C_6)alkyl-C(=O)-OR^5, -NR^5-(C_1-C_6)alkyl-C(=O)-OR^6, -(C_0-C_6)alkyl-C(=O)-R^5, -O-(C_1-C_6)alkyl-C(=O)-R^5, -NR^5-(C_1-C_6)alkyl-C(=O)-R^6, -(C_0-C_6)alkyl-NR^5-C(=O)-OR^6, -(C_0-C_6)alkyl-NR^5-C(=O)-NR^6R^7, -O-(C_2-C_6)alkyl-NR^5-C(=O)-NR^6R^7 and -NR^5-(C_2-C_6)alkyl-NR^6-C(=O)-NR^7R^8;

R^5, R^6, R^7 and R^8 are each independently hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)alkylcyano, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl;

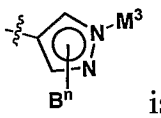
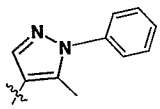
Any two radicals of R (R^5, R^6, R^7 or R^8) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

M^1 is selected from an optionally substituted aryl and heteroaryl;

M^3 is an optionally substituted radical selected from the group of -(C_3-C_7)cycloalkyl, aryl, heteroaryl, heterocycle, -(C_1-C_6)alkyl-R^{11}, -(C_1-C_6)alkylhalo, -(C_2-C_6)alkyl-$NR^{11}R^{12}$, -(C_2-C_6)alkyl-OR^{11} and -(C_2-C_6)alkyl-SR^{11}; and

R^{11} and R^{12} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)alkylcyano, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl;

and provided that according to proviso (v):

when  is  , X^3 is C, n is 1, A^1 is H, then M^1 can not be an optionally substituted aryl, 1-methyl-1H-indazol-4-yl, 1H-indazol-3-yl and 1H-indazol-4-yl;

and provided that according to proviso (vi):

when M^3 is 4-methylphenyl, then B^n can not be a phenyl;

and provided that according to proviso (vii):

when A^1 is different from a pyridyl;

and provided that according to proviso (viii):

when X^3 is C, to provide a thiazole ring, n is 1, then A^1 is not an optionally substituted imidazolyl or triazolyl ring.

In a specific aspect of Formula (III), the invention provides a compound wherein:

A^1 radicals are each independently selected from the group of hydrogen, halogen, -CN, -CF_3, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -

$(C_1\text{-}C_6)$alkylhalo, -$(C_3\text{-}C_7)$cycloalkyl, -$(C_1\text{-}C_6)$alkylcyano, heterocycle, -$(C_0\text{-}C_6)$alkyl-OR^1, -$(C_3\text{-}C_7)$cycloalkyl-$(C_1\text{-}C_6)$alkyl, -NR^1-$(C_3\text{-}C_7)$cycloalkyl-$(C_1\text{-}C_6)$alkyl, -$(C_1\text{-}C_6)$alkylhalo-OR^1, -$(C_1\text{-}C_6)$alkylhalo-NR^1R^2, $(C_0\text{-}C_6)$alkyl-NR^1R^2, -NR^1-$(C_2\text{-}C_6)$alkyl-NR^2R^3, -$(C_0\text{-}C_6)$alkyl-C(=O)-NR^1R^2, -NR^1-$(C_1\text{-}C_6)$alkyl-C(=O)-NR^2R^3, -$(C_0\text{-}C_6)$alkyl-NR^1C(=O)-R^2, -NR^1-$(C_2\text{-}C_6)$alkyl-NR^2C(=O)-R^3, -$(C_0\text{-}C_6)$alkyl-C(=O)-R^1, -NR^1-$(C_1\text{-}C_6)$alkyl-C(=O)-R^2;

R^1, R^2 and R^3 are each independently hydrogen or an optionally substituted radical selected from the group of -$(C_1\text{-}C_6)$alkylhalo, -$(C_1\text{-}C_6)$alkyl, -$(C_3\text{-}C_7)$cycloalkyl, -$(C_4\text{-}C_{10})$alkylcycloalkyl and heterocycle;

Any two radicals of R (R^1, R^2 or R^3) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

B^n radicals are each independently selected from the group of hydrogen, halogen, -CN, -CF_3, and an optionally substituted radical selected from the group of -$(C_1\text{-}C_6)$alkyl, -$(C_1\text{-}C_6)$alkylhalo, -$(C_3\text{-}C_7)$cycloalkyl, -$(C_1\text{-}C_6)$alkylcyano, -$(C_1\text{-}C_6)$alkylheteroaryl, -$(C_1\text{-}C_6)$alkylaryl, aryl, heteroaryl, heterocycle, -$(C_0\text{-}C_6)$alkyl-OR^5, -O-$(C_2\text{-}C_6)$alkyl-OR^5, -$NR^5$$(C_2\text{-}C_6)$alkyl-$OR^6$, -$(C_3\text{-}C_7)$cycloalkyl-$(C_1\text{-}C_6)$alkyl, -O-$(C_3\text{-}C_7)$cycloalkyl-$(C_1\text{-}C_6)$alkyl, -$NR^5$-$(C_3\text{-}C_7)$cycloalkyl-$(C_1\text{-}C_6)$alkyl, -$(C_1\text{-}C_6)$alkylhalo-$OR^5$, -$(C_1\text{-}C_6)$alkylhalo-$NR^5R^6$, -$(C_0\text{-}C_6)$alkyl-S-$R^5$, -O-$(C_2\text{-}C_6)$alkyl-S-$R^5$, -$NR^5$-$(C_2\text{-}C_6)$alkyl-S-$R^6$, -$(C_0\text{-}C_6)$alkyl-S(=O)-$R^5$, -O-$(C_1\text{-}C_6)$alkyl-S(=O)-$R^5$, -$NR^5$-$(C_1\text{-}C_6)$alkyl-S(=O)-$R^6$, -$(C_0\text{-}C_6)$alkyl-$S(=O)_2$-$R^5$, -O-$(C_1\text{-}C_6)$alkyl-$S(=O)_2$-$R^5$, -$NR^5$-$(C_1\text{-}C_6)$alkyl-$S(=O)_2$-$R^6$, -$(C_0\text{-}C_6)$alkyl-$NR^5R^6$, -O-$(C_2\text{-}C_6)$alkyl-$NR^5R^6$, -$NR^5$-$(C_2\text{-}C_6)$alkyl-$NR^6R^7$, -$(C_0\text{-}C_6)$alkyl-$S(=O)_2NR^5R^6$, -O-$(C_1\text{-}C_6)$alkyl-$S(=O)_2NR^5R^6$, -$NR^5$-$(C_1\text{-}C_6)$alkyl-$S(=O)_2NR^6R^7$, -$(C_0\text{-}C_6)$alkyl-$NR^5$-$S(=O)_2R^6$, -O-$(C_2\text{-}C_6)$alkyl-$NR^5$-$S(=O)_2R^6$, -$NR^5$-$(C_2\text{-}C_6)$alkyl-$NR^6$-$S(=O)_2R^7$, -$(C_0\text{-}C_6)$alkyl-C(=O)-$NR^5R^6$, -O-$(C_1\text{-}C_6)$alkyl-C(=O)-$NR^5R^6$, -$NR^5$-$(C_1\text{-}C_6)$alkyl-C(=O)-$NR^6R^7$, -$(C_0\text{-}C_6)$alkyl-$NR^5$C(=O)-$R^6$, -O-$(C_2\text{-}C_6)$alkyl-$NR^5$C(=O)-$R^6$, -$NR^5$-$(C_2\text{-}C_6)$alkyl-$NR^6$C(=O)-$R^7$, -O-$(C_2\text{-}C_6)$alkyl-OC(=O)-$R^5$, -$NR^5$-$(C_2\text{-}C_6)$alkyl-OC(=O)-$R^6$, -$(C_0\text{-}C_6)$alkyl-C(=O)-$OR^5$, -O-$(C_1\text{-}C_6)$alkyl-C(=O)-$OR^5$, -$NR^5$-$(C_1\text{-}C_6)$alkyl-C(=O)-$OR^6$, -$(C_0\text{-}C_6)$alkyl-C(=O)-$R^5$, -O-$(C_1\text{-}C_6)$alkyl-C(=O)-$R^5$, -$NR^5$-$(C_1\text{-}$

C_6)alkyl-C(=O)-R^6, -(C_0-C_6)alkyl-NR^5-C(=O)-OR^6, -(C_0-C_6)alkyl-NR^5-C(=O)-NR^6R^7, -O-(C_2-C_6)alkyl-NR^5-C(=O)-NR^6R^7 and -NR^5-(C_2-C_6)alkyl-NR^6-C(=O)-NR^7R^8;

R^5, R^6, R^7 and R^8 are each independently hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)alkylcyano, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl;

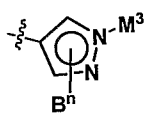
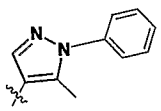
Any two radicals of R (R^5, R^6, R^7 and R^8) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

M^1 is selected from an optionally substituted aryl and heteroaryl;

M^3 is an optionally substituted radical selected from the group of -(C_3-C_7)cycloalkyl, aryl, heteroaryl, heterocycle, -(C_1-C_6)alkyl-R^{11}, -(C_1-C_6)alkylhalo, -(C_2-C_6)alkyl-$NR^{11}R^{12}$, -(C_2-C_6)alkyl-OR^{11} and -(C_2-C_6)alkyl-SR^{11}; and

R^{11} and R^{12} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)alkylcyano, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl;

provided that according to proviso (v):

when  is  , X^3 is C, n is 1, A^1 is H, then M^1 can not be an optionally substituted aryl, 1-methyl-1H-indazol-4-yl, 1H-indazol-3-yl and 1H-indazol-4-yl;

and provided that according to proviso (vi):

when M^3 is 4-methylphenyl, then B^n can not be a phenyl;

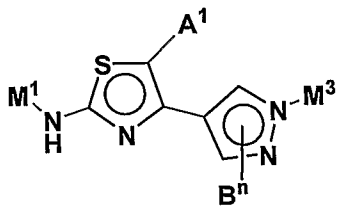
and provided that according to proviso (vii):

A^1 is not a pyridyl;

and provided that according to proviso (viii):

when X^3 is C to provide a thiazole ring, n is 1, then A^1 is not an optionally substituted imidazolyl or triazolyl ring.

In a specific aspect of Formula (III), the invention provides a compound according to Formula (IIIA),



(IIIA)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof, wherein:

A^1 radical is selected from the group of hydrogen, halogen, -CN, -CF_3, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylcyano, heterocycle, -(C_0-C_6)alkyl-OR^1, -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -NR^1-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo-OR^1, -(C_1-C_6)alkylhalo-NR^1R^2, (C_0-C_6)alkyl-NR^1R^2, -NR^1-(C_2-C_6)alkyl-NR^2R^3, -(C_0-C_6)alkyl-C(=O)-NR^1R^2, -NR^1-(C_1-C_6)alkyl-C(=O)-NR^2R^3, -(C_0-C_6)alkyl-NR^1C(=O)-R^2, -NR^1-(C_2-C_6)alkyl-NR^2C(=O)-R^3, -(C_0-C_6)alkyl-C(=O)-R^1, and -NR^1-(C_1-C_6)alkyl-C(=O)-R^2;

R^1, R^2 and R^3 are each independently hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)alkylcyano, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl;

Any two radicals of R (R^1, R^2 and R^3) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

n is an integer ranging from 1 to 2;

B^n radicals are each independently selected from the group of hydrogen, halogen, -CN, $-CF_3$, and an optionally substituted radical selected from the group of -$(C_1$-$C_6)$alkyl, -$(C_1$-$C_6)$alkylhalo, -$(C_3$-$C_7)$cycloalkyl, aryl, heteroaryl, heterocycle, -$(C_0$-$C_6)$alkyl-OR^5, -O-$(C_2$-$C_6)$alkyl-OR^5, -$NR^5(C_2$-$C_6)$alkyl-OR^6, -$(C_3$-$C_7)$cycloalkyl-$(C_1$-$C_6)$alkyl, -O-$(C_3$-$C_7)$cycloalkyl-$(C_1$-$C_6)$alkyl, -NR^5-$(C_3$-$C_7)$cycloalkyl-$(C_1$-$C_6)$alkyl, -$(C_1$-$C_6)$alkylhalo-OR^5, -$(C_1$-$C_6)$alkylhalo-NR^5R^6, -$(C_0$-$C_6)$alkyl-NR^5R^6, -O-$(C_2$-$C_6)$alkyl-NR^5R^6, -NR^5-$(C_2$-$C_6)$alkyl-NR^6R^7, -$(C_0$-$C_6)$alkyl-C(=O)-NR^5R^6, -O-$(C_1$-$C_6)$alkyl-C(=O)-NR^5R^6, -$(C_1$-$C_6)$alkyl-OC(=O)-R^5, -$(C_0$-$C_6)$alkyl-C(=O)-OR^5, -O-$(C_1$-$C_6)$alkyl-C(=O)-OR^5, -NR^5-$(C_1$-$C_6)$alkyl-C(=O)-OR^6, -$(C_0$-$C_6)$alkyl-C(=O)-R^5, -O-$(C_1$-$C_6)$alkyl-C(=O)-R^5 and -NR^5-$(C_1$-$C_6)$alkyl-C(=O)-R^6;

R^5, R^6 and R^7 are each independently hydrogen or an optionally substituted radical selected from the group of -$(C_1$-$C_6)$alkylhalo, -$(C_1$-$C_6)$alkyl, -$(C_1$-$C_6)$alkylcyano, -$(C_3$-$C_7)$cycloalkyl, -$(C_4$-$C_{10})$alkylcycloalkyl, heteroaryl, -$(C_1$-$C_6)$alkylheteroaryl, aryl, heterocycle and -$(C_1$-$C_6)$alkylaryl;

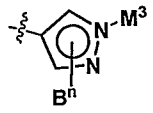
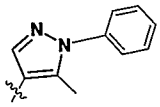
Any two radicals of R (R^5, R^6, or R^7) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

M^1 is selected from an optionally substituted aryl and heteroaryl;

M^3 is an optionally substituted radical selected from the group of -$(C_3$-$C_7)$cycloalkyl, aryl, heteroaryl, heterocycle, -$(C_1$-$C_6)$alkyl-R^{11}, -$(C_1$-$C_6)$alkylhalo, -$(C_2$-$C_6)$alkyl-$NR^{11}R^{12}$, -$(C_2$-$C_6)$alkyl-OR^{11} and -$(C_2$-$C_6)$alkyl-SR^{11}; and

R^{11} and R^{12} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of -$(C_1$-$C_6)$alkylhalo, -$(C_1$-$C_6)$alkyl, -$(C_3$-$C_7)$cycloalkyl, -$(C_4$-$C_{10})$alkylcycloalkyl, heteroaryl, -$(C_1$-$C_6)$alkylheteroaryl, aryl, heterocycle and -$(C_1$-$C_6)$alkylaryl;

provided that according to proviso (v):

when  is  , X^3 is C, n is 1, A^1 is H, then M^1 can not be an optionally substituted aryl, 1-methyl-1H-indazol-4-yl, 1H-indazol-3-yl and 1H-indazol-4-yl;

and provided that according to proviso (vi):

when M^3 is 4-methylphenyl, then B^n can not be a phenyl;

and provided that according to proviso (vii):

A^1 is not a pyridyl;

and provided that according to proviso (viii):

when X^3 is C to provide a thiazole ring, n is 1, then A^1 is not an optionally substituted imidazolyl or triazolyl ring.

In a specific embodiment of the Formula (IIIA),

A^1 radical is selected from the group of hydrogen, halogen, $-CF_3$, and an optionally substituted radical selected from the group of $-(C_1-C_6)$alkyl, $-(C_1-C_6)$alkylhalo, $-(C_3-C_7)$cycloalkyl and heterocycle;

n is an integer ranging from 1 to 2, and either;

(a) n is 1 and B^1 radical is selected from the group of hydrogen, halogen, $-CF_3$, and an optionally substituted radical selected from the group of $-(C_1-C_6)$alkyl, $-(C_1-C_6)$alkylhalo, $-(C_3-C_7)$cycloalkyl, $-(C_0-C_6)$alkyl-OR^5, and $-(C_3-C_7)$cycloalkyl-(C_1-C_6)alkyl; or

(b) n is 2, and B^1 and B^2 radicals are each independently selected from the group of $-CF_3$ and an optionally substituted radical selected from the group of $-(C_1-C_6)$alkyl, $-(C_1-C_6)$alkylhalo, $-(C_3-C_7)$cycloalkyl, and $-(C_3-C_7)$cycloalkyl-(C_1-C_6)alkyl;

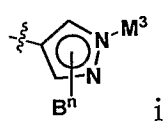
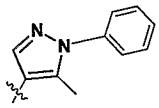
R^5 is selected from the group of hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl and heterocycle;

M^1 is an optionally substituted aryl;

M^3 is an optionally substituted radical selected from the group of -(C_3-C_7)cycloalkyl, aryl, heteroaryl, heterocycle, -(C_1-C_6)alkyl-R^{11}, -(C_1-C_6)alkylhalo, -(C_2-C_6)alkyl-$NR^{11}R^{12}$, -(C_2-C_6)alkyl-OR^{11} and -(C_2-C_6)alkyl-SR^{11};

R^{11} and R^{12} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl;

provided that according to proviso (v):

when  is  , X^3 is C, n is 1, A^1 is H, then M^1 can not be 1-methyl-1H-indazol-4-yl, 1H-indazol-3-yl and 1H-indazol-4-yl;

and provided that according to proviso (vii):

A^1 is not a pyridyl;

and provided that according to proviso (viii):

when X^3 is C, X^4 is C, to provide a thiazole ring, n is 1, then A^1 is not an optionally substituted imidazolyl or triazolyl ring.

In another specific embodiment of the Formula (IIIA),

A^1 radical is selected from the group of hydrogen, halogen, -CF_3, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_3-C_7)cycloalkyl and heterocycle;

n is an integer ranging from 1 to2, and either;

(a) n is 1 and B^1 radical is selected from the group of hydrogen, halogen, $-CF_3$, and an optionally substituted radical selected from the group of $-(C_1-C_6)$alkyl, $-(C_1-C_6)$alkylhalo, $-(C_3-C_7)$cycloalkyl, $-(C_0-C_6)$alkyl-OR^5, and $-(C_3-C_7)$cycloalkyl-(C_1-C_6)alkyl; or

(b) n is 2, and B^1 and B^2 radicals are each independently selected from the group of $-CF_3$ and an optionally substituted radical selected from the group of $-(C_1-C_6)$alkyl, $-(C_1-C_6)$alkylhalo, $-(C_3-C_7)$cycloalkyl, and $-(C_3-C_7)$cycloalkyl-(C_1-C_6)alkyl;

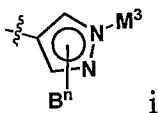
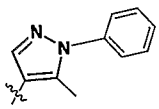
R^5 is selected from the group hydrogen or an optionally substituted radical selected from the group of $-(C_1-C_6)$alkylhalo, $-(C_1-C_6)$alkyl, $-(C_3-C_7)$cycloalkyl, $-(C_4-C_{10})$alkylcycloalkyl and heterocycle;

M^1 is an optionally substituted heteroaryl;

M^3 is an optionally substituted radical selected from the group of $-(C_3-C_7)$cycloalkyl, aryl, heteroaryl, heterocycle, $-(C_1-C_6)$alkyl-R^{11}, $-(C_1-C_6)$alkylhalo, $-(C_2-C_6)$alkyl-$NR^{11}R^{12}$, $-(C_2-C_6)$alkyl-OR^{11} and $-(C_2-C_6)$alkyl-SR^{11};

R^{11} and R^{12} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of $-(C_1-C_6)$alkylhalo, $-(C_1-C_6)$alkyl, $-(C_3-C_7)$cycloalkyl, $-(C_4-C_{10})$alkylcycloalkyl, heteroaryl, $-(C_1-C_6)$alkylheteroaryl, aryl, heterocycle and $-(C_1-C_6)$alkylaryl;

and provided that according to proviso (v):

when  is  , X^3 is C, n is 1, A^1 is H, then M^1 can not be 1-methyl-1H-indazol-4-yl, 1H-indazol-3-yl and 1H-indazol-4-yl;

and provided that according to proviso (vii):

A^1 is not a pyridyl;

and provided that according to proviso (viii):

when X^3 is C to provide a thiazole ring, n is 1, then A^1 is not an optionally substituted imidazolyl or triazolyl ring.

In a more specific embodiment of the Formula (IIIA),

A^1 radical is hydrogen,

n is an integer ranging from 1 to2, and either;

(a) n is 1 and B^1 radical is selected from the group of hydrogen, $-CF_3$, $-(C_1-C_6)$alkyl and $-(C_1-C_6)$alkylhalo; or

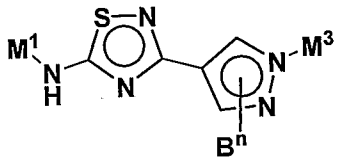
(b) n is 2, and B^1 and B^2 radicals are each independently selected from the group of $-CF_3$ and an optionally substituted radical selected from the group of $-(C_1-C_6)$alkyl and $-(C_1-C_6)$alkylhalo;

M^1 is an optionally substituted pyridyl;

M^3 is an optionally substituted radical selected from the group of $-(C_3-C_7)$cycloalkyl, aryl, heteroaryl, heterocycle, $-(C_1-C_6)$alkyl-R^{11}, $-(C_1-C_6)$alkylhalo, $-(C_2-C_6)$alkyl-$NR^{11}R^{12}$, $-(C_2-C_6)$alkyl-OR^{11} and $-(C_2-C_6)$alkyl-SR^{11}; and

R^{11} and R^{12} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of $-(C_1-C_6)$alkylhalo, $-(C_1-C_6)$alkyl, $-(C_3-C_7)$cycloalkyl, $-(C_4-C_{10})$alkylcycloalkyl, heteroaryl, $-(C_1-C_6)$alkylheteroaryl, aryl, heterocycle and $-(C_1-C_6)$alkylaryl.

In a more specific aspect of Formula (III), the invention provides a compound according to Formula (IIIB),



(IIIB)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof, wherein:

n is an integer ranging from 1 to 2;

B^n radicals are each independently selected from the group of hydrogen, halogen, -CN, $-CF_3$, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_3-C_7)cycloalkyl, aryl, heteroaryl, heterocycle, -(C_0-C_6)alkyl-OR^5, -O-(C_2-C_6)alkyl-OR^5, -NR^5(C_2-C_6)alkyl-OR^6, -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -O-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -NR^5-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo-OR^5, -(C_1-C_6)alkylhalo-NR^5R^6, -(C_0-C_6)alkyl-NR^5R^6, -O-(C_2-C_6)alkyl-NR^5R^6, -NR^5-(C_2-C_6)alkyl-NR^6R^7, -(C_0-C_6)alkyl-C(=O)-NR^5R^6, -O-(C_1-C_6)alkyl-C(=O)-NR^5R^6, -(C_1-C_6)alkyl-OC(=O)-R^5, -(C_0-C_6)alkyl-C(=O)-OR^5, -O-(C_1-C_6)alkyl-C(=O)-OR^5, -NR^5-(C_1-C_6)alkyl-C(=O)-OR^6, -(C_0-C_6)alkyl-C(=O)-R^5, -O-(C_1-C_6)alkyl-C(=O)-R^5 and -NR^5-(C_1-C_6)alkyl-C(=O)-R^6;

R^5, R^6 and R^7 are each independently hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)alkylcyano, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl;

Any two radicals of R (R^5, R^6, or R^7) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

M^1 is selected from an optionally substituted aryl and heteroaryl;

M^3 is an optionally substituted radical selected from the group of -(C_3-C_7)cycloalkyl, aryl, heteroaryl, heterocycle, -(C_1-C_6)alkyl-R^{11}, -(C_1-C_6)alkylhalo, -(C_2-C_6)alkyl-$NR^{11}R^{12}$, -(C_2-C_6)alkyl-OR^{11} and -(C_2-C_6)alkyl-SR^{11}; and

R^{11} and R^{12} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl.

In a specific embodiment of the Formula (IIIB),

n is an integer ranging from 1 to 2, and either;

(a) n is 1 and B^1 radical is selected from the group of hydrogen, halogen, -CF_3, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_3-C_7)cycloalkyl, -(C_0-C_6)alkyl-OR^5, aryl, heteroaryl, and -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl; or

(b) n is 2, and B^1 and B^2 radicals are each independently selected from the group of -CF_3 and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_3-C_7)cycloalkyl, and -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl;

R^5 is selected from the group hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl and heterocycle;

M^1 is an optionally substituted aryl;

M^3 is an optionally substituted radical selected from the group of -(C_3-C_7)cycloalkyl, aryl, heteroaryl, heterocycle, -(C_1-C_6)alkyl-R^{11}, -(C_1-C_6)alkylhalo, -(C_2-C_6)alkyl-$NR^{11}R^{12}$, -(C_2-C_6)alkyl-OR^{11} and -(C_2-C_6)alkyl-SR^{11}; and

R^{11} and R^{12} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl,

-(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl.

In another specific embodiment of the Formula (IIIB),

n is an integer ranging from 1 to 2, and either;

(a) n is 1 and B^1 radical is selected from the group of hydrogen, halogen, -CF_3, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_3-C_7)cycloalkyl, -(C_0-C_6)alkyl-OR^5, aryl, heteroaryl, and -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl; or

(b) n is 2, and B^1 and B^2 radicals are each independently selected from the group of -CF_3 and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_3-C_7)cycloalkyl, and -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl;

R^5 is selected from the group hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl and heterocycle;

M^1 is an optionally substituted heteroaryl;

M^3 is an optionally substituted radical selected from the group of -(C_3-C_7)cycloalkyl, aryl, heteroaryl, heterocycle, -(C_1-C_6)alkyl-R^{11}, -(C_1-C_6)alkylhalo, -(C_2-C_6)alkyl-$NR^{11}R^{12}$, -(C_2-C_6)alkyl-OR^{11} and -(C_2-C_6)alkyl-SR^{11}; and

R^{11} and R^{12} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl.

In a more specific embodiment of the Formula (IIIB),

n is an integer ranging from 1 to 2, and either;

(a) n is 1 and B^1 radical is selected from the group of hydrogen, $-CF_3$, $-(C_1-C_6)$alkyl and $-(C_1-C_6)$alkylhalo; or

(b) n is 2, and B^1 and B^2 radicals are each independently selected from the group of $-CF_3$ and an optionally substituted radical selected from the group of $-(C_1-C_6)$alkyl and $-(C_1-C_6)$alkylhalo;

M^1 is an optionally substituted pyridyl;

M^3 is an optionally substituted radical selected from the group of $-(C_3-C_7)$cycloalkyl, aryl, heteroaryl, heterocycle, $-(C_1-C_6)$alkyl-R^{11}, $-(C_1-C_6)$alkylhalo, $-(C_2-C_6)$alkyl-$NR^{11}R^{12}$, $-(C_2-C_6)$alkyl-OR^{11} and $-(C_2-C_6)$alkyl-SR^{11}; and

R^{11} and R^{12} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of $-(C_1-C_6)$alkylhalo, $-(C_1-C_6)$alkyl, $-(C_3-C_7)$cycloalkyl, $-(C_4-C_{10})$alkylcycloalkyl, heteroaryl, $-(C_1-C_6)$alkylheteroaryl, aryl, heterocycle and $-(C_1-C_6)$alkylaryl.

Specific compounds of the invention according to Formula (I) to (III) are compounds as mentioned in the following list A and list B as well as a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof:

List A:

3-(1,3-Dimethyl-1*H*-pyrazol-4-yl)-*N*-methyl-*N*-phenyl-1,2,4-thiadiazol-5-amine

3-(1,5-Dimethyl-1*H*-pyrazol-4-yl)-*N*-methyl-*N*-phenyl-1,2,4-thiadiazol-5-amine

N-(2-Fluorophenyl)-3-(1-(4-methoxybenzyl)-3-methyl-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

N-(2-Fluorophenyl)-3-(1-(4-methoxybenzyl)-5-methyl-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

3-(1-(4-Methoxybenzyl)-3-methyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-(4-Methoxybenzyl)-5-methyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-

thiadiazol-5-amine

3-(1-(4-Methoxybenzyl)-1*H*-pyrazol-4-yl)-*N*-phenyl-1,2,4-thiadiazol-5-amine

4-(1-(4-Methoxybenzyl)-3-methyl-1H-pyrazol-4-yl)-N-phenylthiazol-2-amine

4-(1-(4-Methoxybenzyl)-5-methyl-1H-pyrazol-4-yl)-N-phenylthiazol-2-amine

3-(5-Methyl-1-phenyl-1*H*-pyrazol-4-yl)-*N*-phenyl-1,2,4-thiadiazol-5-amine

3-(3-Methyl-1-propyl-1*H*-pyrazol-4-yl)-*N*-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine

4-(1-Benzyl-1H-pyrazol-4-yl)-N-phenylthiazol-2-amine

4-(1-Isopropyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)thiazol-2-amine

4-(1-Ethyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)thiazol-2-amine and

4-(1-Methyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)thiazol-2-amine.

List B:

4-(1-Propyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)thiazol-2-amine

N-(Benzo[d][1,3]dioxol-5-yl)-4-(1-propyl-1H-pyrazol-4-yl)thiazol-2-amine

N-(2-Fluorophenyl)-4-(1-propyl-1H-pyrazol-4-yl)thiazol-2-amine

4-(3-Methyl-1-propyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)thiazol-2-amine

4-(3-Methyl-1-propyl-1H-pyrazol-4-yl)-N-(6-methylpyridin-2-yl)thiazol-2-amine

N-(5-Chloropyridin-2-yl)-4-(3-methyl-1-propyl-1H-pyrazol-4-yl)thiazol-2-amine

N-(6-Methoxypyridin-3-yl)-4-(3-methyl-1-propyl-1H-pyrazol-4-yl)thiazol-2-amine

N-(2-Methoxypyridin-3-yl)-4-(3-methyl-1-propyl-1H-pyrazol-4-yl)thiazol-2-amine

4-(1-Propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)thiazol-2-amine

4-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)thiazol-2-amine

N-(Pyridin-2-yl)-4-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)thiazol-2-amine

3-(1-Ethyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-Ethyl-1H-pyrazol-4-yl)-N-(6-methoxypyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-Ethyl-1H-pyrazol-4-yl)-N-(6-morpholinopyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-Ethyl-3-methyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-Propyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-(3-Fluorobenzyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-(3-Fluorobenzyl)-1H-pyrazol-4-yl)-N-phenyl-1,2,4-thiadiazol-5-amine

N-(Pyridin-2-yl)-3-(1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(pyridine-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine hydrochloride

3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(6-methylpyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(6-ethylpyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(6-fluoropyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(5-fluoropyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(6-methoxypyridin-2-yl)-1,2,4-thiadiazol-5-amine

N-(6-Cyclobutoxypyridin-2-yl)-3-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(6-morpholinopyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(5-morpholinopyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(6-(trifluoromethyl)pyridin-2-yl)-1,2,4-thiadiazol-5-amine

N-(5-Chloropyridin-2-yl)-3-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

6-(3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-ylamino)nicotinonitrile

3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(pyrazin-2-yl)-1,2,4-thiadiazol-5-amine

6-(3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-ylamino)nicotinamide

3-(1-(Cyclobutylmethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-(2-Morpholinoethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine

N-(Pyridin-2-yl)-3-(1-((tetrahydrofuran-2-yl)methyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

N-(Pyridin-2-yl)-3-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

3-(1-(2-Methoxyethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine

2-(4-(5-(Pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)-1H-pyrazol-1-yl)ethanol

3-(1-Cyclobutyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-(3-Fluoro-4-methoxyphenyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-(4-Fluorophenyl)-5-methyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-(4-Fluorophenyl)-5-methyl-1H-pyrazol-4-yl)-N-phenyl-1,2,4-thiadiazol-5-amine

3-(1-Propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine

N-(6-Methylpyridin-2-yl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

N-(6-Methoxypyridin-3-yl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

N-(2-Methoxypyridin-3-yl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

N-(5-Chloropyridin-2-yl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

3-(1-Propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)-1,2,4-thiadiazol-5-amine

N-(3,5-Difluoropyridin-2-yl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

3-(1-Propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-N-(quinolin-2-yl)-1,2,4-thiadiazol-5-amine

N-(2-Methylpyridin-4-yl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

N-(2-Fluorophenyl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

N-(2,5-Difluorophenyl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

N-(Benzo[d][1,3]dioxol-5-yl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

N-(4-Morpholinophenyl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

N-(3-Methoxyphenyl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

3-(1-Propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-N-(3-(trifluoromethyl)phenyl)-1,2,4-thiadiazol-5-amine

N-(4-Chlorophenyl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

3-(1-(Cyclopropylmethyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine

N-(Pyridin-2-yl)-3-(1-(2,2,2-trifluoroethyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

3-(3,5-Dimethyl-1-propyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-(Cyclopropylmethyl)-3,5-dimethyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-(Cyclopropylmethyl)-3,5-dimethyl-1H-pyrazol-4-yl)-N-(6-methylpyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(3-Methyl-1-propyl-1H-pyrazol-4-yl)-N-(6-methylpyridin-2-yl)-1,2,4-thiadiazol-5-amine

N-(6-Ethylpyridin-2-yl)-3-(3-methyl-1-propyl-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-

amine
3-(3-Methyl-1-propyl-1H-pyrazol-4-yl)-N-(6-(trifluoromethyl)pyridin-2-yl)-1,2,4-thiadiazol-5-amine
3-(3-Methyl-1-propyl-1H-pyrazol-4-yl)-N-(3-(trifluoromethyl)pyridin-2-yl)-1,2,4-thiadiazol-5-amine
N-(5-Chloropyridin-2-yl)-3-(3-methyl-1-propyl-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine
N-(5-Fluoropyridin-2-yl)-3-(3-methyl-1-propyl-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine
6-(3-(3-Methyl-1-propyl-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-ylamino)nicotinonitrile
3-(3-Methyl-1-propyl-1H-pyrazol-4-yl)-N-(6-morpholinopyridin-2-yl)-1,2,4-thiadiazol-5-amine
N-(6-Methoxypyridin-2-yl)-3-(3-methyl-1-propyl-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine
N-(6-Fluoropyridin-2-yl)-3-(3-methyl-1-propyl-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine and
3-(3-methyl-1-propyl-1H-pyrazol-4-yl)-N-(pyridin-3-yl)-1,2,4-thiadiazol-5-amine.

DEFINITION OF TERMS

Listed below are definitions of various terms used in the specification and claims to describe the present invention.

For the avoidance of doubt it is to be understood that in this specification "(C_1-C_6)" means a carbon radical having 1, 2, 3, 4, 5 or 6 carbon atoms. "(C_0-C_6)" means a carbon radical having 0, 1, 2, 3, 4, 5 or 6 carbon atoms. In this specification "C" means a carbon atom, "N" means a nitrogen atom, "O" means an oxygen atom and "S" means a sulphur atom.

In the case where a subscript is the integer 0 (zero) the radical to which the subscript refers, indicates that the radical is absent, i.e. there is a direct bond between the radicals.

In this specification, unless stated otherwise, the term "bond" refers to a saturated covalent bond. When two or more bonds are adjacent to one another, they are assumed to be equal to one bond. For example, a radical -A-B-, wherein both A and B may be a bond, the radical is depicting a single bond.

In this specification, unless stated otherwise, the term "alkyl" includes both straight and branched chain alkyl radicals and may be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, t-pentyl, neo-pentyl, n-hexyl, i-hexyl or t-hexyl. The term "(C_0-C_3)alkyl" refers to an alkyl radical having 0, 1, 2 or 3 carbon atoms and may be methyl, ethyl, n-propyl and i-propyl.

In this specification, unless stated otherwise, the term "cycloalkyl" refers to an optionally substituted carbocycle containing no heteroatoms, including mono-, bi-, and tricyclic saturated carbocycles, as well as fused ring systems. Such fused ring systems can include one ring that is partially or fully unsaturated such as a benzene ring to form fused ring systems such as benzo- fused carbocycles. Cycloalkyl includes such fused ring systems as spirofused ring systems. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decahydronaphthalene, adamantane, indanyl, fluorenyl and 1,2,3,4-tetrahydronaphthalene and the like. The term "(C_3-C_7)cycloalkyl" may be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like.

In this specification, unless stated otherwise, the term "alkenyl" includes both straight and branched chain alkenyl radicals. The term "(C_2-C_6)alkenyl" refers to an alkenyl radical having 2 to 6 carbon atoms and one or two double bonds, and may be, but is not limited to vinyl, allyl, propenyl, i-propenyl, butenyl, i-butenyl, crotyl, pentenyl, i-

pentenyl and hexenyl.

In this specification, unless stated otherwise, the term "alkynyl" includes both straight and branched chain alkynyl radicals. The term (C_2-C_6)alkynyl having 2 to 6 carbon atoms and one or two triple bonds, and may be, but is not limited to ethynyl, propargyl, butynyl, i-butynyl, pentynyl, i-pentynyl and hexynyl.

The term "aryl" refers to an optionally substituted monocyclic or bicyclic hydrocarbon ring system containing at least one unsaturated aromatic ring. Examples and suitable values of the term "aryl" are phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, indyl, indenyl, benzo[d][1,3]dioxolyl and the like.

In this specification, unless stated otherwise, the term "heteroaryl" refers to an optionally substituted monocyclic or bicyclic unsaturated, aromatic ring system containing at least one heteroatom selected independently from N, O or S. Examples of "heteroaryl" may be, but are not limited to thienyl, pyridyl, thiazolyl, isothiazolyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxadiazolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolonyl, oxazolonyl, thiazolonyl, tetrazolyl, thiadiazolyl, benzoimidazolyl, benzoxazolyl, benzothiazolyl, tetrahydrotriazolopyridyl, tetrahydrotriazolopyrimidinyl, benzofuryl, benzothiophenyl, thionaphthyl, indolyl, isoindolyl, pyridonyl, pyridazinyl, pyrazinyl, pyrimidinyl, quinolyl, quinolinyl, phtalazinyl, naphthyridinyl, quinoxalinyl, quinazolyl, imidazopyridyl, oxazolopyridyl, thiazolopyridyl, imidazopyridazinyl, oxazolopyridazinyl, thiazolopyridazinyl, cynnolyl, pteridinyl, furazanyl, benzotriazolyl, pyrazolopyridinyl and purinyl. Examples of pyrazolyl may be, but not limited to, 1H-pyrazol-4-yl. Examples of pyridinyl may be, but not limited to, pyridin-2-yl, pyridin-3-yl and pyridin-4-yl.

In this specification, unless stated otherwise, the term "alkylaryl", "alkylheteroaryl" and "alkylcycloalkyl" refers respectively to a substituent that is attached via the alkyl radical to an aryl, heteroaryl or cycloalkyl radical, respectively. The term "(C_1-C_6)alkylaryl" includes aryl-C_1-C_6-alkyl radicals such as benzyl, 1-phenylethyl, 2-phenylethyl, 1-phenylpropyl, 2-phenylpropyl, 3-phenylpropyl, 1-naphthylmethyl and 2-naphthylmethyl. The term "(C_1-C_6)alkyheteroaryl" includes heteroaryl-C_1-C_6-alkyl radicals, wherein examples of heteroaryl are the same as those illustrated in the above definition, such as 2-furylmethyl, 3-furylmethyl, 2-thienylmethyl, 3-thienylmethyl, 1-imidazolylmethyl, 2-imidazolylmethyl, 3-imidazolylmethyl, 2-oxazolylmethyl, 3-oxazolylmethyl, 2-thiazolylmethyl, 3-thiazolylmethyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 1-quinolylmethyl or the like.

In this specification, unless stated otherwise, the term "heterocycle" refers to an optionally substituted, monocyclic or bicyclic saturated, partially saturated or unsaturated ring system (containing at least one heteroatom selected independently from N, O and S. The said "heterocycle" refers respectively to a group linked either via the carbon or the nitrogen. The term "heterocycle" includes morpholine, thiomorpholine, tetrahydrofuran, tetrahydropyran radicals or the like.

In this specification, unless stated otherwise, the term "alkylheterocycle" refers respectively to a substituent that is attached via the alkyl radical to a heterocycle radical, respectively. The term "(C_1-C_6)alkyl heterocycle" includes heterocycle-C_1-C_6-alkyl radicals such as (tetrahydro-2H-pyran-4-yl)methyl, (tetrahydrofuran-2-yl)methyl or morpholinoethyl.

In this specification, unless stated otherwise, a 5- or 6-membered ring containing one or more atoms independently selected from C, N, O and S, includes aromatic and heteroaromatic rings as well as carbocyclic and heterocyclic rings which may be saturated or unsaturated. Examples of such rings may be, but are not limited to, furyl, isoxazolyl, isothiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl,

pyrrolyl, thiazolyl, thienyl, imidazolyl, imidazolidinyl, imidazolinyl, triazolyl, morpholinyl, piperazinyl, piperidyl, piperidonyl, pyrazolidinyl, pyrazolinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, tetrahydrothiopyranyl, oxazolidinonyl, thiomorpholinyl, oxadiazolyl, thiadiazolyl, tetrazolyl, phenyl, cyclohexyl, cyclopentyl, cyclohexenyl and cyclopentenyl.

In this specification, unless stated otherwise, a 3- to 10-membered ring containing one or more atoms independently selected from C, N, O and S, includes aromatic and heteroaromatic rings as well as carbocyclic and heterocyclic rings which may be saturated or unsaturated. Examples of such rings may be, but are not limited to imidazolidinyl, imidazolinyl, morpholinyl, piperazinyl, piperidyl, piperidonyl, pyrazolidinyl, pyrazolinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, thiomorpholinyl, tetrahydrothiopyranyl, furyl, pyrrolyl, isoxazolyl, isothiazolyl, oxazolyl, oxazolidinonyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, thiazolyl, thienyl, imidazolyl, triazolyl, phenyl, cyclopropyl, aziridinyl, cyclobutyl, azetidinyl, oxadiazolyl, thiadiazolyl, tetrazolyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, cyclooctyl and cyclooctenyl.

In this specification, unless stated otherwise, the term "halo" or "halogen" may be fluoro, chloro, bromo or iodo.

In this specification, unless stated otherwise, the term "alkylhalo" means an alkyl radical as defined above, substituted with one or more halo radicals. The term "(C_1-C_6)alkylhalo" may include, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl and trifluoroethyl. The term "O-C_1-C_6-alkylhalo" may include, but is not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy and fluoroethoxy.

In this specification, unless stated otherwise, the term "alkylcyano" means an alkyl radical as defined above, substituted with one or more cyano.

In this specification, unless stated otherwise, the term "optionally substituted" refers to radicals further bearing one or more substituents which may be, but are not limited to, (C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, hydroxy, (C_1-C_6)alkyloxy, mercapto, aryl, heterocycle, halogen, trifluoromethyl, pentafluoroethyl, cyano, cyanomethyl, nitro, amino, amido, amidinyl, carboxyl, carboxamide, (C_1-C_6)alkyloxycarbonyl, carbamate, sulfonamide, ester and sulfonyl. As an example, an optionally substituted (C_1-C_6)alkyl radical, such as a methyl group, by a (C_3-C_7)cycloalkyl, such as cyclopropyl, refers to a cyclopropylmethyl radical. In some examples, pyridyl radicals substituted in the 3-position carboxyl, cyano and carboxamide group may be called nicotinic, nicotinotrile and nicotinamide radicals.

In this specification, unless stated otherwise, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (e.g. a compound of Formula (I)) and a solvent. The solvent is a pharmaceutically acceptable solvent as preferably water; such solvent may not interfere with the biological activity of the solute.

In this specification, unless stated otherwise, the term "antagonists of A_3 refers also to a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof.

PHARMACEUTICAL COMPOSITIONS

Antagonists of A_3 described herein, and the pharmaceutically acceptable salts, solvates and hydrates thereof can be used in pharmaceutical preparations in combination with a pharmaceutically acceptable carrier or diluent. Suitable pharmaceutically acceptable

carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. The antagonists of A_3 will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described herein. Techniques for formulation and administration of the compounds of the instant invention can be found in *Remington: the Science and Practice of Pharmacy*, 19th edition, Mack Publishing Co., Easton, PA (1995).

The amount of antagonists of A_3 receptor, administered to the subject will depend on the type and severity of the disease or condition and on the characteristics of the subject, such as general health, age, sex, body weight and tolerance to drugs. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. Effective dosages for commonly used CNS drugs are well known to the skilled person. The total daily dose usually ranges from about 0.05 – 2000 mg.

The present invention relates to pharmaceutical compositions which provide from about 0.01 to 1000 mg of the active ingredient per unit dose. The compositions may be administered by any suitable route. For example orally in the form of capsules, etc..., parenterally in the form of solutions for injection, topically in the form of unguents or lotions, ocularly in the form of eye-drops, rectally in the form of suppositories, intranasally or transcutaneously in the form of delivery system like patches.

For oral administration, the antagonists of A_3 receptor thereof can be combined with a suitable solid or liquid carrier or diluent to form capsules, tablets, pills, powders, syrups, solutions, suspensions and the like.

The tablets, pills, capsules, and the like contain from about 0.01 to about 99 weight percent of the active ingredient and a binder such as gum tragacanth, acacias, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid, a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

For parenteral administration the disclosed antagonists of A_3 can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. For example, solutions in sesame or peanut oil, aqueous propylene glycol and the like can be used, as well as aqueous solutions of water-soluble pharmaceutically-acceptable salts of the compounds. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

In addition, to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation, for example, subcutaneously or intramuscularly or by intramuscular injection. Thus, for example, as an emulsion in acceptable oil, or ion exchange resins, or as sparingly soluble derivatives, for example, as sparingly soluble salts.

The antagonists of A_3 receptor described herein, and their pharmaceutically acceptable salts, can be incorporated into various types of ophthalmic formulations for delivery to the eye (e.g., topically, intracamerally, or via an implant). Such compounds are preferably incorporated into topical ophthalmic formulations for delivery to the eye. The compounds may be combined with ophthalmologically acceptable preservatives, surfactants, viscosity enhancers, penetration enhancers, buffers, sodium chloride, and water to form an aqueous, sterile ophthalmic suspension or solution. Ophthalmic solution formulations may be prepared by dissolving a compound in a physiologically acceptable isotonic aqueous buffer. Further, the ophthalmic solution may include an ophthalmologically acceptable surfactant to assist in dissolving the compound. In

addition, the ophthalmic solution may contain an agent to increase viscosity, such as, hydroxymethylcellulose, methylcellulose, polyvinylpyrrolidone, and the like, to improve the retention of the formulation in the conjunctival sac. Gelling agents can also be used, such as xanthan gum. In order to prepare sterile ophthamic ointment formulations, the active ingredient is combined with a preservative in an appropriate vehicle, such as, mineral oil or liquid lanolin. Sterile ophthalmic gel formulations may be prepared by suspending the compound in a hydrophilic base, according to the published formulations for analogous ophthalmic preparations. Some preservatives and tonicity agents can be incorporated.

The antagonists of A_3 receptor described herein can be formulated as topical ophthalmic suspensions or solutions, with a pH of about 4 to 8. Such compounds will normally be contained in these formulations in an amount 0.01% to 5% by weight. The dosage form may be a solution, suspension, or microemulsion. For topical presentation 1 to 2 drops of these formulations would be delivered to the surface of the eye 1 to 4 times per day according to the discretion of a skilled clinician.

Preferably disclosed antagonists of A_3 or pharmaceutical formulations containing these compounds are in unit dosage form for administration to a mammal. The unit dosage form can be any unit dosage form known in the art including, for example, a capsule, an IV bag, a tablet, or a vial. The quantity of active ingredient in a unit dose of composition is an effective amount and may be varied according to the particular treatment involved. It may be appreciated that it may be necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration which may be by a variety of routes including oral, aerosol, rectal, transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal, intraocular, eye drop and intranasal.

METHODS OF SYNTHESIS

The compounds according to the invention, in particular the compounds according to the Formula (I), (II), (III), (IIIA) and (IIIB) may be prepared by methods known in the art of organic synthesis as set forth in part by the following synthesis schemes. In all of the schemes described below, it is well understood that protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles of chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (Green T.W. and Wuts P.G.M. (1991) *Protecting Groups in Organic Synthesis*, John Wiley & Sons). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection of process as well as the reaction conditions and order of their execution shall be consistent with the preparation of compounds of Formula (I), (II), (III), (IIIA) and (IIIB).

The compounds according to the invention may be represented as a mixture of enantiomers, which may be resolved into the individual pure *R*- or *S*-enantiomers. If for instance, a particular enantiomer is required, it may be prepared by asymmetric synthesis or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group such as an amino or an acidic functional group such as carboxyl, this resolution may be conveniently performed by fractional crystallization from various solvents as the salts of an optical active acid or by other methods known in the literature (e.g. chiral column chromatography).

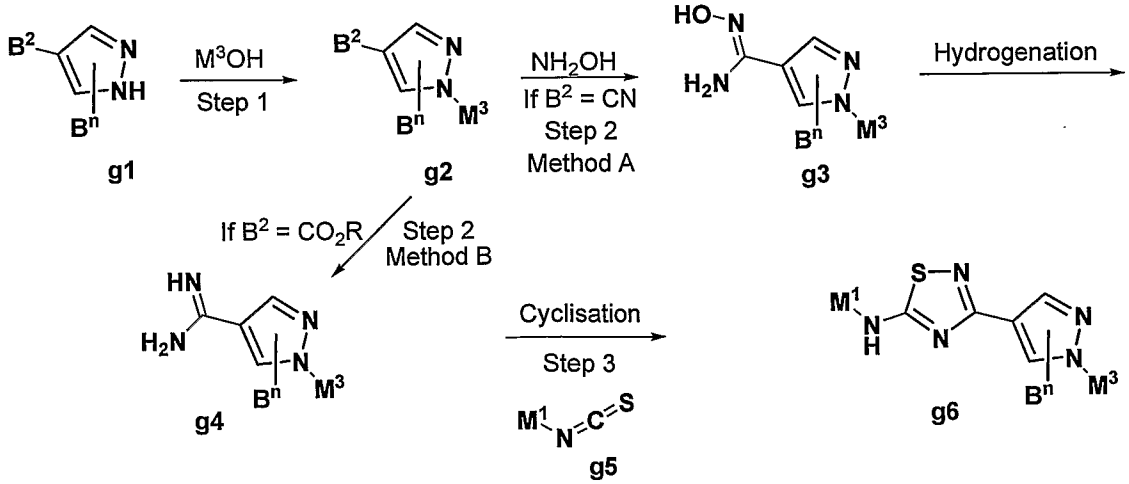
Resolution of the final product, an intermediate or a starting material may be performed by any suitable method known in the art (Eliel E.L., Wilen S.H. and Mander L.N. (1984) *Stereochemistry of Organic Compounds*, Wiley-Interscience).

Many of the heterocyclic compounds of the invention can be prepared using synthetic routes well known in the art (Katrizky A.R. and. Rees C.W. (1984) *Comprehensive Heterocyclic Chemistry*, Pergamon Press).

The product from the reaction can be isolated and purified employing standard techniques, such as extraction, chromatography, crystallization and distillation.

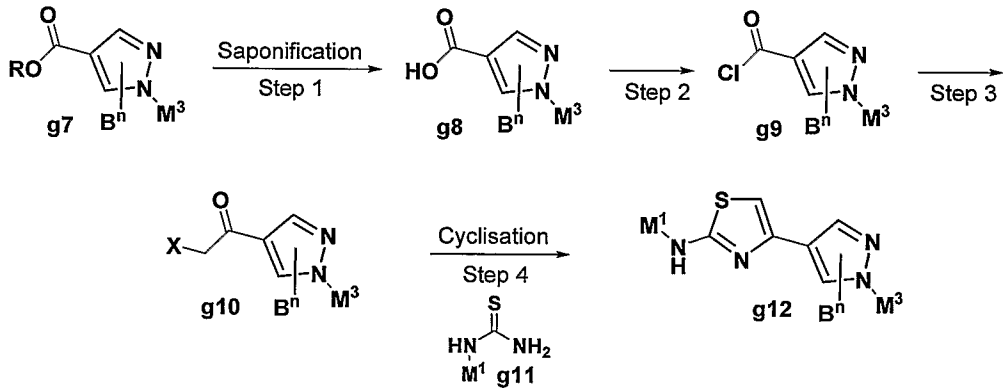
The compounds of the invention may be prepared by general route of synthesis as disclosed in the following methods or according to any method known from the man skilled in the art.

In one embodiment of the present invention compounds of Formula (III) and (IIIB) may be prepared according to the synthetic sequences illustrated in Scheme 1. Pyrazole **g1** can be substituted using Mitsunobu conditions. Then amidine can be synthesized either from ester treated with aluminium chloride in the presence of ammonium chloride or from nitrile by synthesis of amidoxime **g3** followed by hydrogenation, in the presence of Pd/C and anhydride acetic. Finally, the cyclization between the amidine **g4** and the isothiocyanate **g5** may be promoted by di-*tert*-butylazodicarboxylate and a base such as DBU.



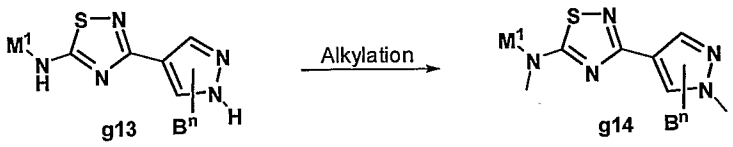
Scheme 1

In another embodiment of the present invention, the compounds of Formula (III) and (IIIA) may be prepared according to the synthetic sequences illustrated in Scheme 2. Compound **g7** may be hydrolyzed by standard procedures followed by reaction with oxalyl chloride to yield compound **g9**. Subsequently, the acid chloride can be transformed in halo-ketone **g10** (sometime present as a mixture of chloro (X=Cl) and bromo (X=Br) derivative) *via* the formation of diazoketone. Finally the cyclization reaction may be performed between the halo-ketone **g10** and the thiourea **g11** to yield the aminothiazole **g12**. Thioureas **g11** can be prepared form the corresponding isothiocyanates **g5** by reaction with methanolic ammonia. When isothiocyanate **g5** was not commercially available or known in the literature, it was prepared from the corresponding amine by treatment either with TDCI (M.P.Gauthier at al (2006) Biorg. Med. Chem. 14: H918-H927) or with thiophosgene (R. D.Haugwitz et al (1985) J. Med. Chem. 9: H1234-H1241) as described in literature.



Scheme 2

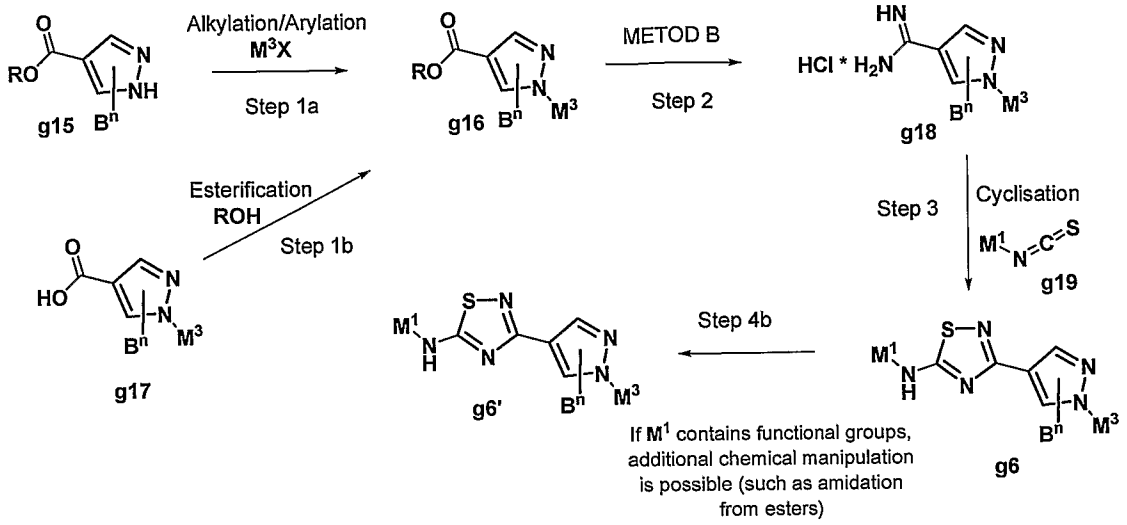
In one embodiment of the present invention, the compounds of Formula (II) may be prepared according to the synthetic sequences illustrated in Scheme 3. Aminothiadiazole **g13** can be alkylated into **g14** in the presence of a base such as NaH and a solvent such as THF.



Scheme 3

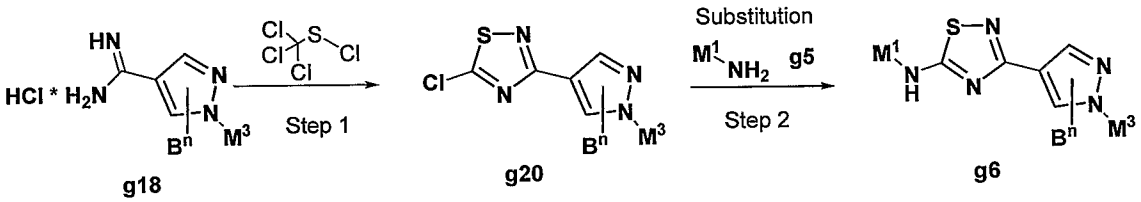
In another embodiment of the present invention, the compounds of Formula (III) and (IIIB) may be prepared according to the synthetic sequences illustrated in Scheme 4. Pyrazole **g15** can be alkylated using the proper alkyl halide, such as bromide and iodide, or triflate in presence of an inorganic base, such as potassium carbonate, in a suitable organic solvent. Alternativerly pyrazole **g15** can be arylated using the proper aryl halide in the presence of an inorganic base, such as potassium carbonate, a copper catalyst, such as copper iodide, a proper ligand, such as 1,10-phenanthroline, in a suitable organic solvent, such as dioxane (Y-M. Zhu at al (2007) Tetrahedron Lett. 48: H6262-H6266).Compound **g16** can be alternatively obtained by esterification of the corresponding commercially available acids **g17** using standard procedures. Then amidine **g18** is synthesized from the corresponding ester by reaction with aluminium chloride in the presence of ammonium chloride in a suitable solvent, such as toluene. The cyclization between the amidine **g18** and the isothiocyanate **g19** is promoted by di-*tert*-butylazodicarboxylate and a base such as DBU, to provide compound **g6**.

When in **M1** is present an additional functional group, such as an ester, it could be converted into a different related residue such as acide or amide by standard procedures known by those skilled in the art, to provide **g6'**.



Scheme 4

In another embodiment of the present invention, the compounds of Formula (III) and (IIIB) may be prepared according to the synthetic sequences illustrated in Scheme 5. Compound **g18**, prepared as described in Scheme 4, can be converted into compound **g20** by cyclization using trichloromethanesulfenyl chloride.in presence of an inorganic base, such as sodium hydroxide, in water. Compound **g20** can be converted to compound **g6** by substitution with the desired amine in presence of a suitable base, such as potassium *tert*-butoxide, in a suitable solvent (dioxane) under reflux.



Scheme 5

EXPERIMENTAL

Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification.

Specifically, the following abbreviations may be used in the examples and throughout the specification.

AcOEt (Ethyl acetate)	$MgSO_4$ (Magnesium sulphate)
BBr_3 (Boron tribromide)	µL(Microliters)
$(Boc)_2O$ (Di-*tert*-butyl carbonate)	mL (Milliliters)
DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene)	mmol (Millimoles)
DCM (Dichloromethane)	Mp (Melting point)
DIEA (Diisopropyl ethyl amine)	NaCl (Sodium chloride)
DMAP (*N*,*N*-Dimethylaminopyridine)	NaH (Sodium hydride)
DMF (Dimethylformamide)	NaOH (Sodium hydroxide)
Et_2O (Diethyl ether)	Na_2SO_4 (Sodium sulphate)
EtOH (Ethanol)	NH_4OH (Ammonium hydroxide)
HBr (Hydrobromic acid)	Pd (Palladium)
HCl (Hydrochloric acid)	PCl_5 (Phosphorus pentachloride)
K_2CO_3 (Potassium carbonate)	$POCl_3$ (Phosphorus oxychloride)
LCMS (Liquid Chromatography Mass Spectrum)	TEA (Triethyl amine)
LiOH (Lithium hydroxide)	TFA (Trifluoroacetic acid)
M (Molar)	THF (Tetrahydrofuran)
MeOH (Methanol)	TLC (Thin layer chromatography)
mg (Milligrams)	RT (Retention Time)
$NaHCO_3$ (Sodium hydrogenocarbonate)	

All references to brine refer to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions are conducted not under an inert atmosphere at room temperature unless otherwise noted.

Most of the reaction were monitored by thin-layer chromatography on 0.25mm Merck silica gel plates (60F-254), visualized with UV light. Flash column chromatography was performed on silica gel (40-63 µM, Merck) or on prepacked silica gel cartridges (15-40 µM, Merck or 40-63 µM, Biotage).

Melting point determination was performed on a Buchi B-540 apparatus.

^1H NMR spectra were recorded on a Brucker 300MHz (see Table 4). Chemical shifts are expressed in parts of million (ppm, δ units). Coupling constants are in units of herts

(Hz) Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quadruplet), quint (quintuplet), m (multiplet), br (broad). Mobile protons are omitted for some products.

Physico-Chemical Data

LCMS chromatograms were recorded under the following conditions:

Method LC-A:

Waters Micromass ZQ 2996 system

Reversed phase HPLC was carried out on an Zorbax SB-C18 cartridge (1.8 µm, 4.6 x 30 mm) from Agilent, with a flow rate of 1.5 ml/min. The gradient conditions used are: 90 % A (water + 0.05 % of formic acid), 10% B (acetonitrile + 0.05 % of formic acid) to 100 % B at 3.5 minutes, kept till 3.7 minutes and equilibrated to initial conditions at 3.8 minutes until 4.5 minutes. Injection volume 5-20 µL.

Method LC-B:

Waters Acquity UPLC Micromass ZQ 2000 Single quadrupole

Reversed phase HPLC was carried out on a Acquity UPLC-BEH C18 cartridge (1.7µm, 50x2.1mm) from Waters, with a flow rate of 0.5 ml/min. The gradient conditions used are: Mobile phase: A phase= water/CH_3CN 95/5 + 0.1% TFA; B phase= water/CH_3CN 5/95 + 0.1% TFA. 0-0.30min (A: 92%, B: 8%), 0.30-1.50 min (A: 0%, B: 100%), 1.50-2.00 min (A: 0%, B: 100%), 2.00-2.40 min (A: 95%, B: 5%). Injection volume 2µl

Method LC-C

Waters Acquity UPLC Micromass ZQ 2000 Single quadrupole

Reversed phase HPLC was carried out on a Acquity UPLC-BEH C18 cartridge (1.7µm, 50x2.1mm) from Waters, with a flow rate of 0.5 ml/min. The gradient conditions used

are: Mobile phase: A phase= water/CH_3CN 95/5 + 0.1% TFA; B phase= water/CH_3CN 5/95 + 0.1% TFA. 0-0.30min (A: 95%, B: 5%), 0.30-3.30 min (A: 0%, B: 100%), 3.30-3.90 min (A: 0%, B: 100%), 3.90-4.40 min (A: 95%, B: 5%). Injection volume 2µl

Method LC-D

LCMS were recorded on a Waters Acquity UPLC Micromass ZQ 2000 Single quadrupole system by the following conditions:

Reversed phase HPLC was carried out on a Acquity UPLC-BEH C18 cartridge (1.7µm, 50x2.1mm) from Waters, with a flow rate of 0.5 ml/min. The gradient conditions used are: Mobile phase: A phase= water/CH_3CN 95/5 + 0.1% TFA; B phase= water/CH_3CN 5/95 + 0.1% TFA. 0-0.10min (A: 95%, B: 5%), 0.10-1.40 min (A: 0%, B: 100%), 1.40-1.90 min (A: 0%, B: 100%), 1.90-2.40 min (A: 95%, B: 5%). Injection volume 2µl

Method LC-E

Waters Acquity UPLC Micromass ZQ 2000 Single quadrupole

Reversed phase HPLC was carried out on a Acquity UPLC-BEH C18 cartridge (1.7µm, 50x2.1mm) from Waters, with a flow rate of 0.6 ml/min. The gradient conditions used are: Mobile phase: A phase= water/CH_3CN 95/5 + 0.1% TFA; B phase= water/CH_3CN 5/95 + 0.1% TFA. 0-0.25min (A: 95%, B: 5%), 0.25-3.30 min (A: 0%, B: 100%), 3.30-4.00 min (A: 0%, B: 100%), 4.00-4.10 min (A: 95%, B: 5%), 4.10-5.00 min (A: 95%, B: 5%). Injection volume 2µl

Method LC-F

Waters Acquity UPLC Micromass ZQ 2000 Single quadrupole

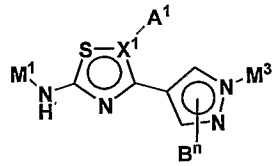
Reversed phase HPLC was carried out on a Acquity UPLC-BEH C18 cartridge (1.7µm, 50x2.1mm) from Waters, with a flow rate of 0.6 ml/min. The gradient conditions used are: Mobile phase: A phase= water/CH_3CN 95/5 + 0.1% TFA; B phase= water/CH_3CN 5/95 + 0.1% TFA. 0-0.50min (A: 95%, B: 5%), 0.50-6.00 min (A: 0%, B: 100%), 6.00-

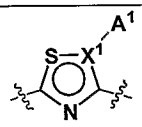
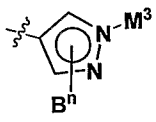
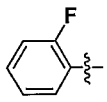
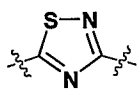
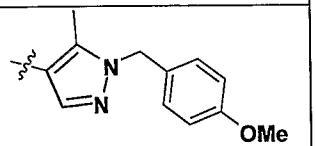
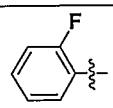
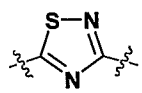
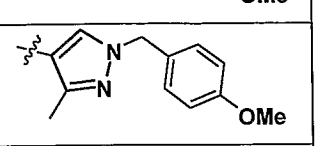
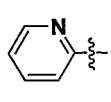
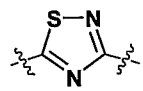
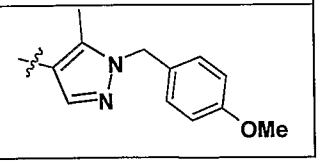
7.00 min (A: 0%, B: 100%), 7.00-7.10 min (A: 95%, B: 5%); 7.10-8.50 min (A: 95%, B: 5%); Injection volume: 2µl

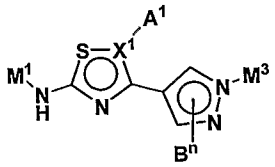
ES MS detector was used, acquiring both in positive and negative ionization modes. Cone voltages were 30 V (Method LC-A), 26V (Methods LC-B, LC-C and LC-D) and 25V (Methods LC-E and LC-F) for both positive and negative ionization modes.All mass spectra were taken under electrospray ionisation (ESI) methods (see Table 3).

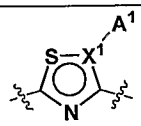
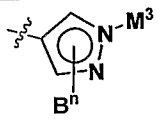
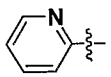
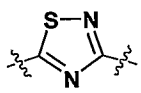
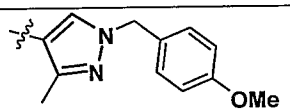
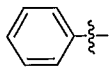
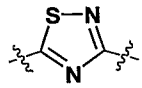
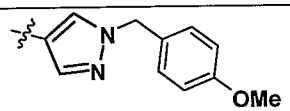
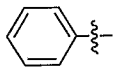
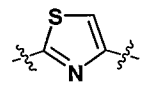
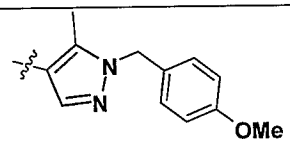
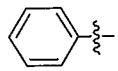
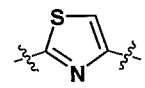
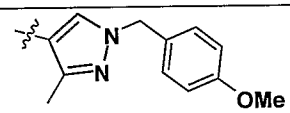
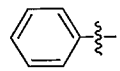
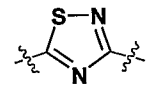
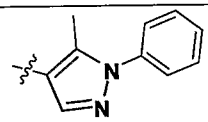
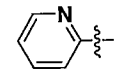
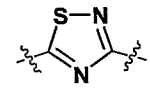
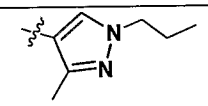
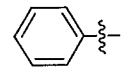
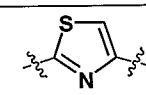
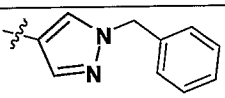
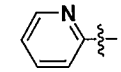
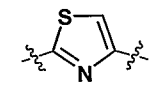
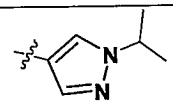
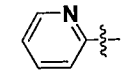
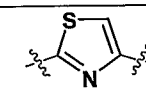
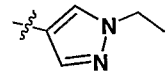
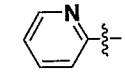
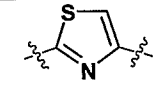
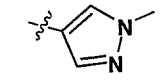
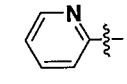
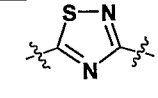
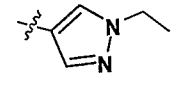
The compounds (Cpd) in the following Tables have been synthezised according to the same methods as previous examples 1 to 11, as denoted in the column denoted as "Exp. nr". The compounds denoted with the asterisk have been exemplified in the Examples.

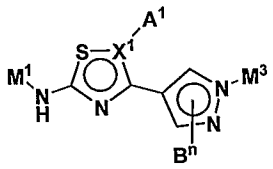
Table 1: Compounds prepared according to the Examples.

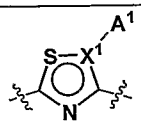
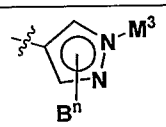
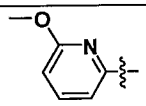
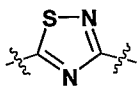
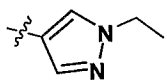
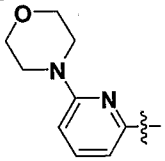
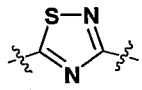
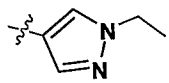
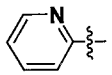
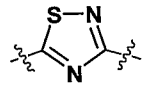
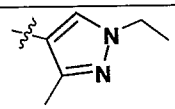
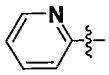
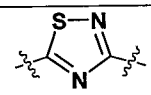
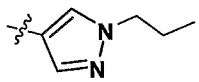
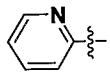
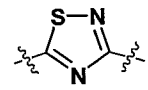
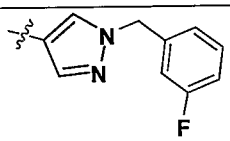
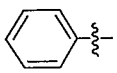
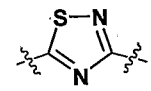
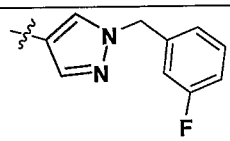
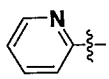
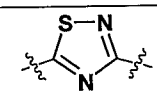
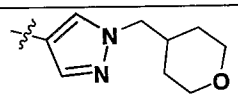
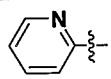
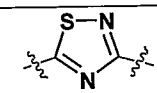
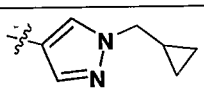
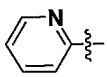
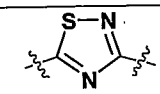
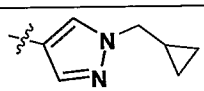
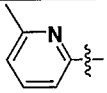
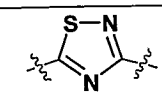
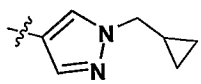


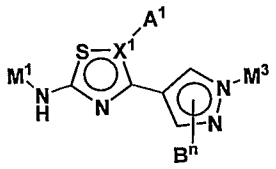
Cpd	Exp nr.	M^1		
1-1*	1			
1-2*	1			
1-3	1			

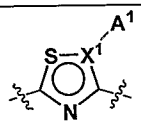
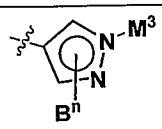
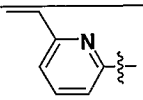
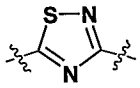
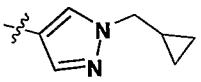
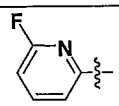
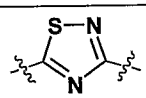
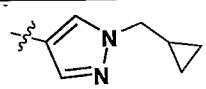
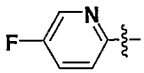
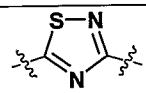
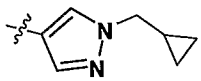
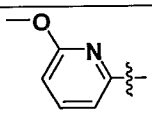
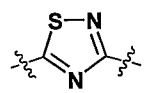
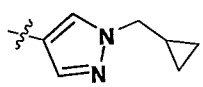
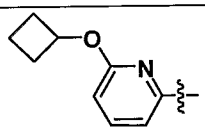
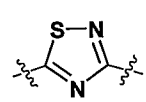
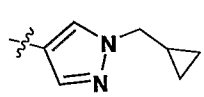
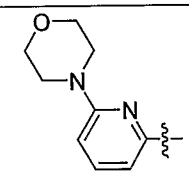
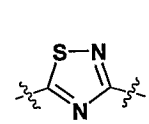
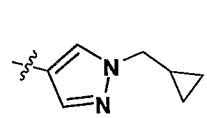
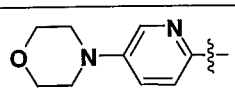
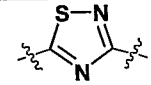
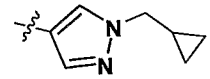
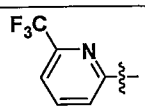
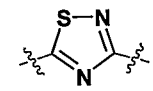
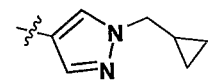
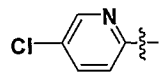
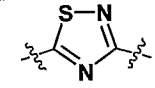
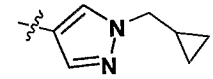
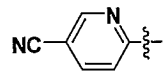
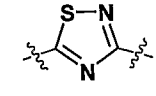
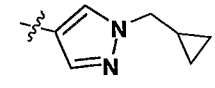
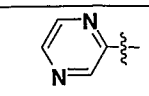
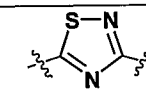
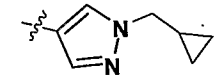


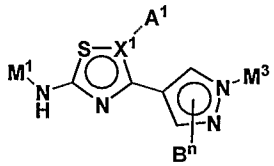
Cpd	Exp nr.	M^1		
1-4	1			
1-5	1			
1-6	3			
1-7	3			
1-8*	2			
1-9	2			
1-10	3			
1-11*	3			
1-12	3			
1-13	3			
1-14	5			

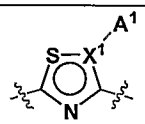
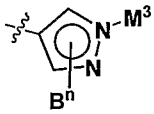
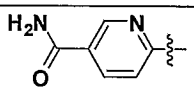
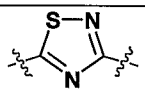
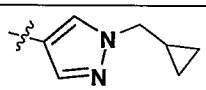
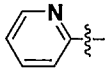
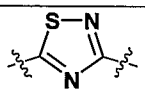
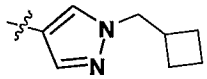
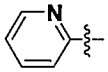
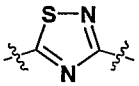
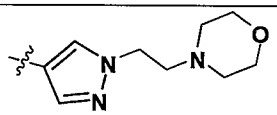
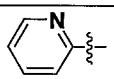
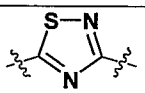
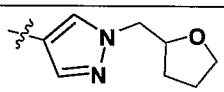
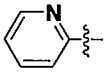
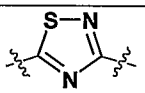
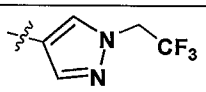
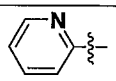
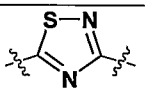
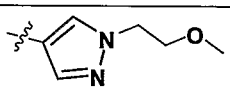
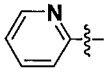
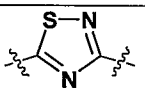
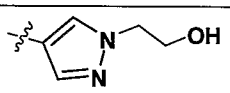
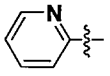
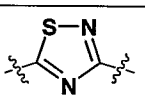
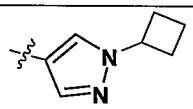
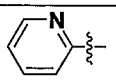
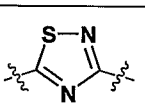
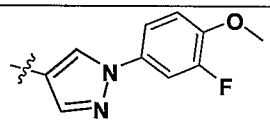
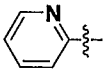
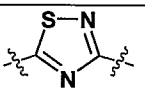
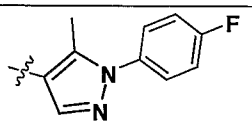
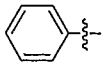
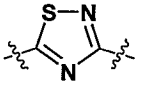
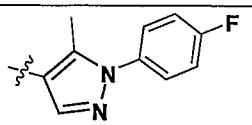


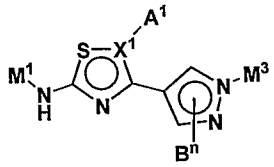
Cpd	Exp nr.	M^1		
1-15	5			
1-16	5			
1-17*	6			
1-18	5			
1-19	5			
1-20	5			
1-21	5			
1-22*	5			
1-22a*	5			
1-23	5			

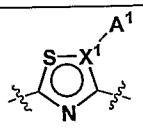
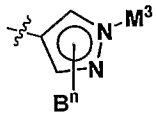
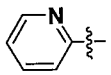
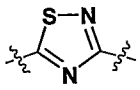
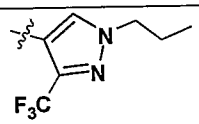
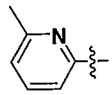
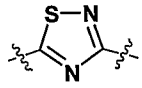
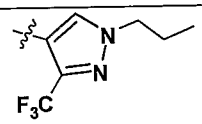
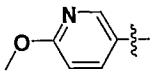
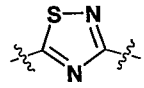
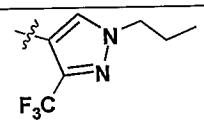
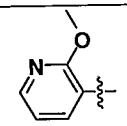
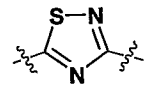
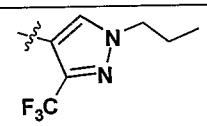
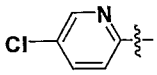
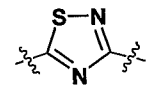
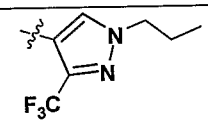
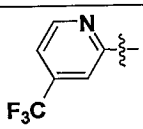
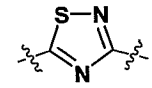
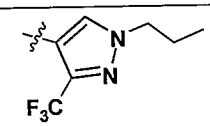
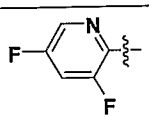
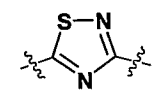
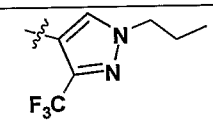
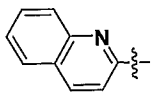
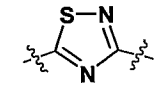
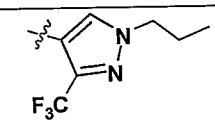
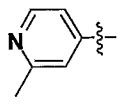
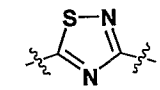
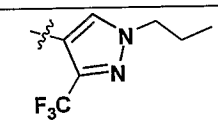
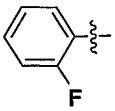
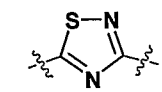
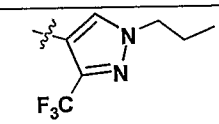


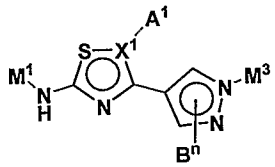
Cpd	Exp nr.	M^1		
1-24	5			
1-25	5			
1-26	5			
1-27	5			
1-28	5			
1-29	5			
1-30	5			
1-31	5			
1-32	5			
1-33*	8			
1-34	8			

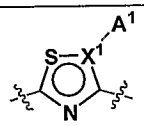
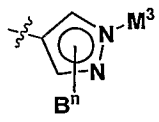
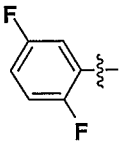
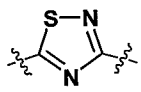
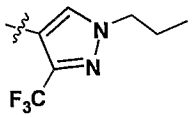
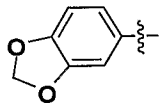
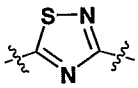
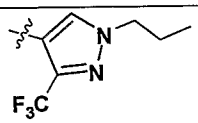
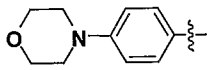
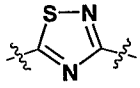
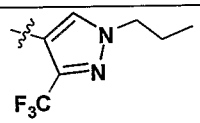
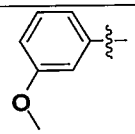
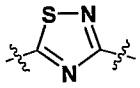
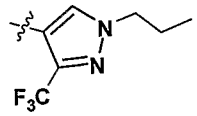
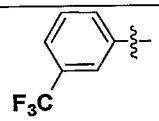
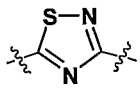
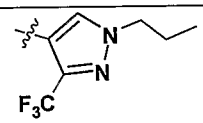
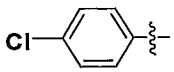
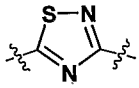
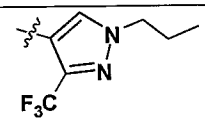
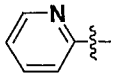
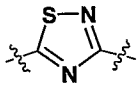
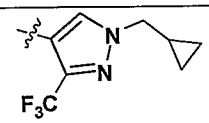
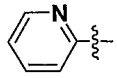
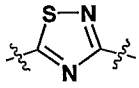
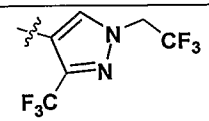
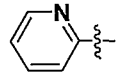
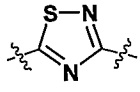
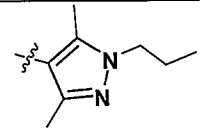


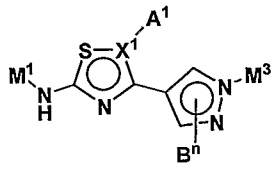
Cpd	Exp nr.	M^1		
1-35*	10			
1-36	5			
1-37	5			
1-38	5			
1-39	5			
1-40	5			
1-41*	9			
1-42	5			
1-43*	7			
1-44	6			
1-45	6			

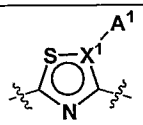
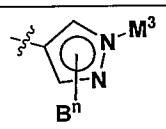
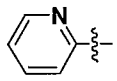
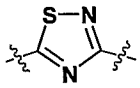
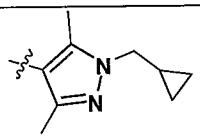
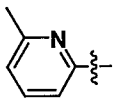
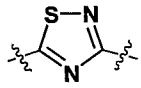
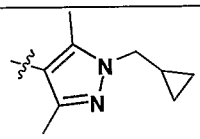
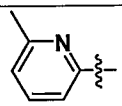
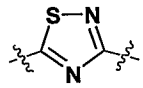
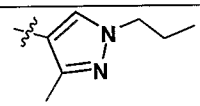
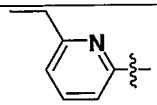
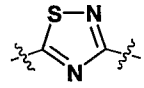
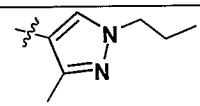
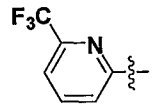
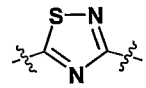
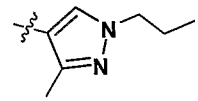
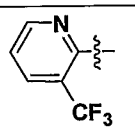
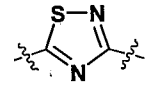
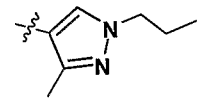
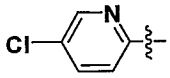
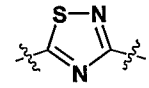
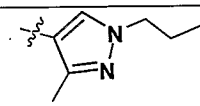
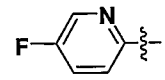
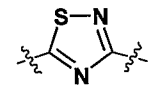
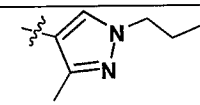
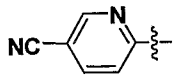
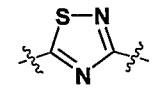
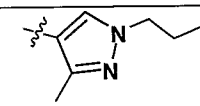
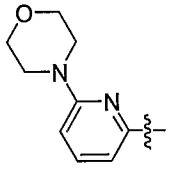
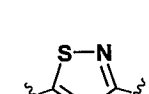
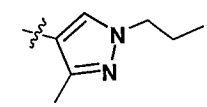


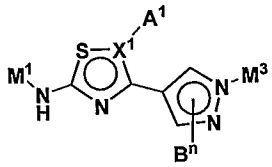
Cpd	Exp nr.	M^1		
1-46	5			
1-47	5			
1-48	5			
1-49	5			
1-50	5			
1-51	5			
1-52	5			
1-53	5			
1-54	5			
1-55	5			

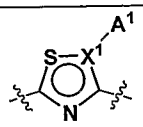
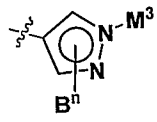
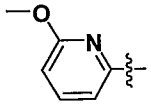
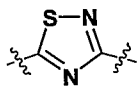
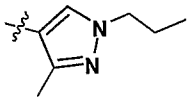
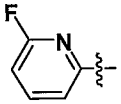
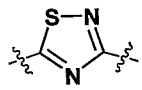
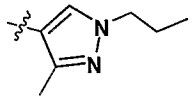
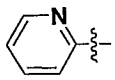
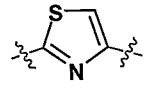
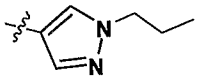
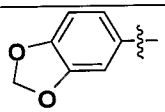
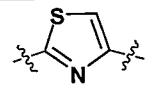
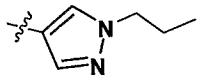
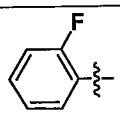
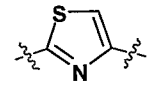
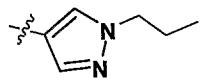
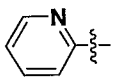
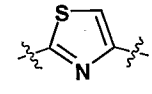
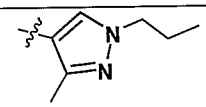
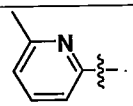
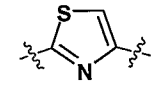
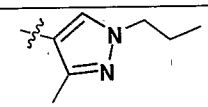
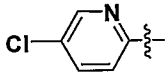
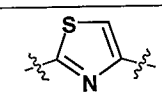
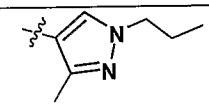
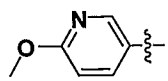
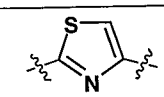
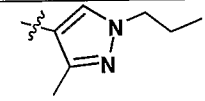
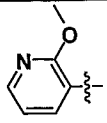
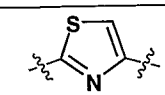
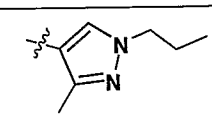


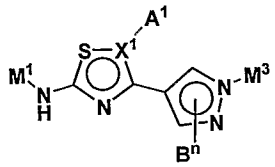
Cpd	Exp nr.	M^1		
1-56	5			
1-57	5			
1-58	5			
1-59	5			
1-60	5			
1-61	5			
1-62	5			
1-63	5			
1-64	5			



Cpd	Exp nr.	M^1		
1-65	5			
1-66	5			
1-67	6			
1-68	6			
1-69	6			
1-70	6			
1-71	6			
1-72	6			
1-73	6			
1-74	6			



Cpd	Exp nr.	M^1		
1-75	6			
1-76	6			
1-77	11			
1-78	11			
1-79	11			
1-80	11			
1-81	11			
1-82	11			
1-83	11			
1-84	11			



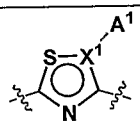
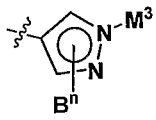
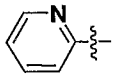
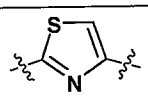
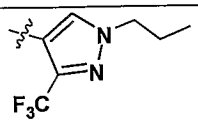
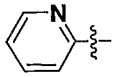
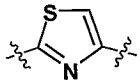
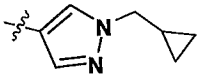
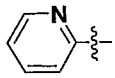
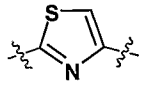
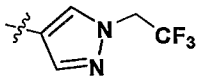
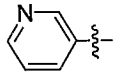
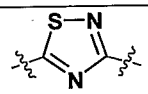
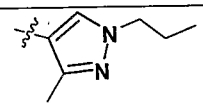
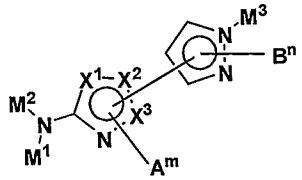
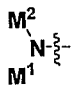
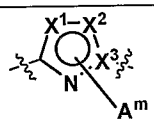
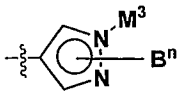
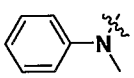
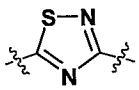
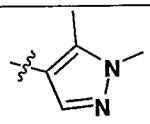
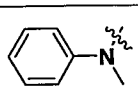
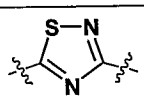
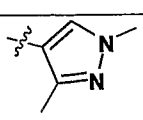
Cpd	Exp nr.	M^1		
1-85	11			
1-86	11			
1-87*	11			
1-88	2			

Table 2: Compounds prepared according to the Examples.



Cpd	Exp nr.			
2-1*	4			
2-2*	4			

EXAMPLES

KAS/ClientDocs/Addex/53195.WO01.FinalSpec.10.07 2008

EXAMPLE 1: *N*-(2-Fluorophenyl)-3-(1-(4-methoxybenzyl)-3-methyl-1*H*-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine and *N*-(2-fluorophenyl)-3-(1-(4-methoxybenzyl)-5-methyl-1*H*-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine (Final Compounds 1-1 and 1-2)

1.1: 1-(4-Methoxybenzyl)-3-methyl-1H-pyrazole-4-carbonitrile and 1-(4-methoxybenzyl)-5-methyl-1H-pyrazole-4-carbonitrile

According to Scheme 1 Step 1 of the general methodology: Triphenylphosphine (11 mmol, 2.9 g), (4-methoxyphenyl)methanol (10 mmol, 1.4 g) and di-*tert*-butylazodicarboxylate (11 mmol, 2.6 g) were added to a solution of 3-methyl-1*H*-pyrazole-4-carbonitrile (9.3 mmol, 1.0 g), in DCM (40 mL) at 0°C. The reaction mixture was stirred at room temperature overnight. The organic phase was washed with a saturated solution of NH_4OH and brine. Then the organic phase was dried over $MgSO_4$, was filtered and was concentrated under reduced pressure. The resulting crude product was purified by flash chromatography over silica gel using cyclohexane/AcOEt (90:10) as eluent to yield 1-(4-methoxybenzyl)-3-methyl-1*H*-pyrazole-4-carbonitrile and 1-(4-methoxybenzyl)-5-methyl-1*H*-pyrazole-4-carbonitrile (9.3 mmol, 2.1g, 100%).

1.2: 1-(4-Methoxybenzyl)-3-methyl-1H-pyrazole-4-carboximidamide and 1-(4-methoxybenzyl)-5-methyl-1H-pyrazole-4-carboximidamide

According to Scheme 1 Step 2 of the general methodology, Method A: A mixture of 1-(4-methoxybenzyl)-3-methyl-1*H*-pyrazole-4-carbonitrile and 1-(4-methoxybenzyl)-5-methyl-1*H*-pyrazole-4-carbonitrile (9.90 mmol, 2.25 g), hydroxylamine 50% in water (19.8 mmol, 1.21 mL) and EtOH (10 mL) was heated at 80°C for 12 hours. After evaporation of the solvent, 2.42 g (9.30 mmol, 94%) of *N*'-hydroxy-1-(4-methoxybenzyl)-3-methyl-1*H*-pyrazole-4-carboximidamide and *N*'-hydroxy-1-(4-methoxybenzyl)-5-methyl-1*H*-pyrazole-4-carboximidamide were obtained. The crude product was used in the next step without purification.

LC (Method LC-A): RT = 0.86 min; MS *m/z* ES^+= 261.

A mixture of *N'*-hydroxy-1-(4-methoxybenzyl)-3-methyl-1*H*-pyrazole-4-carboximidamide and *N'*-hydroxy-1-(4-methoxybenzyl)-5-methyl-1*H*-pyrazole-4-carboximidamide (9.30 mmol, 2.42 g), Pd/C (200 mg) and anhydride acetic (9.30 mmol, 0.88 mL) in MeOH (30 mL) was stirred at room temperature for 13 hours under hydrogen atmosphere. After filtration and evaporation of the solvent, the crude product was triturated with Et_2O and dried to yield 1-(4-methoxybenzyl)-3-methyl-1*H*-pyrazole-4-carboximidamide and 1-(4-methoxybenzyl)-5-methyl-1*H*-pyrazole-4-carboximidamide (1.55 g, 5.11 mmol, 55%) as a white solid.

LC (Method LC-A): RT = 0.91 min; MS *m/z* ES^+= 245.

According to Scheme 1 Step 3 of the general methodology, DBU (0.39 mmol, 60.0 mg) was added to a solution of 1-fluoro-2-isothiocyanatobenzene (0.39 mmol, 48 µl) and 1-(4-methoxybenzyl)-3-methyl-1*H*-pyrazole-4-carboximidamide and 1-(4-methoxybenzyl)-5-methyl-1*H*-pyrazole-4-carboximidamide (0.39 mmol, 200 mg) in DMF (7 mL) under nitrogen. The reaction mixture was stirred at room temperature until total consumption of the amidine. Then, di-*tert*-butylazodicarboxylate (0.43 mmol, 100 mg) was added dropwise and the reaction mixture was stirred for 5 minutes. After evaporation of the EtOH, water was added and the aqueous phase was extracted with AcOEt. The organic phase was washed with a solution of HCl 1 M, water and brine, was dried over Na_2SO_4, was filtered and was concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel using cyclohexane/AcOEt (80:20) as eluent to afford *N*-(2-fluorophenyl)-3-(1-(4-methoxybenzyl)-3-methyl-1*H*-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine and *N*-(2-fluorophenyl)-3-(1-(4-methoxybenzyl)-5-methyl-1*H*-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine (0.13 mmol, 50 mg, 32%) as a white solid.

LC (Method LC-A): RT = 2.80 min; MS *m/z* ES^+= 396.

EXAMPLE 2: 3-(5-Methyl-1-phenyl-1*H*-pyrazol-4-yl)-*N*-phenyl-1,2,4-thiadiazol-5-amine (Final Compound 1-8)

2.1: 5-Methyl-1-phenyl-1H-pyrazole-4-carboximidamide

According to Scheme 1 Step 2 of the general methodology, Method B: Trimethylaluminium, 2M solution in heptane (21.7 mmol, 10.9 mL), was added dropwise to a suspension of ammonium chloride (21.7 mmol, 1.16 g) in dry toluene (20 mL), under an argon atmosphere, at 0°C. The reaction mixture was stirred at room temperature until no more evolution of gas was observed. After addition of 5-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic acid ethyl ester (2.17 mmol, 500 mg), the reaction mixture was stirred at 80°C overnight. The reaction mixture was then cooled down to 0°C and MeOH was added with consequent stirring for 1 hour at room temperature. The reaction mixture was added to a mixture of DCM and silica, then filtered on an empty cartridge. The cartridge was first eluted with DCM and then with DCM/MeOH (80:20) as eluent. After filtration and evaporation, 5-methyl-1-phenyl-1*H*-pyrazole-4-carboximidamide (1.55 mmol, 310 mg, 71%) was obtained as a white solid.

LC (Method LC-A): RT = 0.91 min; MS *m/z* ES^+= 201.

2.2: 3-(5-Methyl-1-phenyl-1H-pyrazol-4-yl)-N-phenyl-1,2,4-thiadiazol-5-amine

According to Scheme 1 Step 3 of the general methodology: DBU (0.42 mmol, 64 mg) was added to a solution of 5-methyl-1-phenyl-1*H*-pyrazole-4-carboximidamide (0.42 mmol, 100 mg) and isothiocyanatobenzene (0.42 mmol, 57 mg) in dry DMF (5 mL), under argon. The reaction mixture was stirred at room temperature until total consumption of the amidine. Then, di-*tert*-butylazodicarboxylate (0.42 mmol, 97 mg) was added dropwise and was stirred for 5 minutes. The reaction mixture was quenched with water and was extracted with AcOEt. The organic phase was washed with brine, was dried over Na_2SO_4, was filtered and was concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel using

cyclohexane/AcOEt (80:20) as eluent to afford 3-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-*N*-phenyl-1,2,4-thiadiazol-5-amine (0.22 mmol, 75 mg, 53%) as a white powder.

LC (Method LC-A): RT = 2.85 min; MS *m/z* ES^- = 332.

EXAMPLE 3: 4-(1-Isopropyl-1*H*-pyrazol-4-yl)-*N*-(pyridin-2-yl)thiazol-2-amine (Final Compound 1-11)

3.1: 1-Isopropyl-1H-pyrazole-4-carboxylic acid

According to Scheme 2 Step 1 of the general methodology: A solution of ethyl 1-isopropyl-1*H*-pyrazole-4-carboxylate (2.28 mmol, 417 mg) and LiOH (23.4 mmol, 1.00 g) in water/MeOH (1:1, 10 mL) was heated at 90°C overnight. After evaporation of the solvent, the aqueous phase was extracted with DCM then acidified with a solution of HCl 1 M until pH = 1-2 and extracted with DCM. The organic phase was washed with brine, was dried over Na_2SO_4, was filtered and was concentrated under reduced pressure to yield 1-isopropyl-1*H*-pyrazole-4-carboxylic acid (1.95 mmol, 300 mg, 85%) as a white solid. The crude product was used without purification.

LC (Method LC-A): RT = 1.07 min; MS *m/z* ES^- = 155.

3.2: 1-Isopropyl-1H-pyrazole-4-carbonyl chloride

According to Scheme 2 Step 2: of the general methodology A solution of 1-isopropyl-1*H*-pyrazole-4-carboxylic acid (1.95 mmol, 300 mg), oxalyl chloride (3.42 mmol, 0.30 mL) and three drops of DMF in DCM (5 mL) was stirred for 2 hours at room temperature. After evaporation of the solvent, the crude residue was treated with toluene and was coevaporated to dryness to yield 1-isopropyl-1*H*-pyrazole-4-carbonyl chloride (1.95 mmol, 0.33 g). The crude product was used without purification.

LC (Method LC-A): RT = 1.58 min.

3.3: 2-Bromo-1-(1-isopropyl-1H-pyrazol-4-yl)ethanone

According to Scheme 2 Step 3 of the general methodology: A solution of TMSdiazomethane (6.0 mmol, 3.0 mL) was added to a solution of 1-isopropyl-1*H*-pyrazole-4-carbonyl chloride (1.95 mmol, 0.33 g) in acetonitrile (5 mL) at 0°C. The reaction mixture was stirred at room temperature overnight. HBr (8.0 mmol, 0.9 mL, 48%) was added at 0°C to the reaction mixture. The reaction mixture was stirred at room temperature for one hour. After evaporation of the solvent, AcOEt was added and the aqueous phase was neutralized with a solution of NaOH 1 M. The aqueous phase was extracted with AcOEt. The organic phase was washed with brine, was dried over Na_2SO_4, was filtered and was concentrated under reduced pressure to yield 2-bromo-1-(1-isopropyl-1*H*-pyrazol-4-yl)ethanone (1.95 mmol, 0.45 g, 100%) as an orange oil. The crude product was used without purification.

3.4: 4-(1-Isopropyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)thiazol-2-amine

According to Scheme 2 Step 4 of the general methodology: A solution of 2-bromo-1-(1-isopropyl-1*H*-pyrazol-4-yl)ethanone (0.43 mmol, 0.10 g) and of 1-(pyridin-2-yl)thiourea (0.35 mmol, 53 mg) in acetone (5 mL) was stirred under reflux for one hour. After evaporation of the solvent, DCM was added and the organic phase was washed with a saturated solution of $NaHCO_3$, water and brine. The organic phase was dried over Na_2SO_4, was filtered and was concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel using DCM/AcOEt (90:10) as eluent to yield 4-(1-isopropyl-1*H*-pyrazol-4-yl)-*N*-(pyridin-2-yl)thiazol-2-amine (0.32 mmol, 92 mg) as a white solid.

LC (Method LC-A): RT = 1.91 min; MS *m/z* ES^+= 286.

EXAMPLE 4: 3-(1,3-Dimethyl-1*H*-pyrazol-4-yl)-*N*-methyl-*N*-phenyl-1,2,4-thiadiazol-5-amine and 3-(1,5-dimethyl-1*H*-pyrazol-4-yl)-*N*-methyl-*N*-phenyl-1,2,4-thiadiazol-5-amine (Final Compounds 2-1 and 2-2)

According to Scheme 3 of the general methodology: NaH (0.97 mmol, 42 mg) was added to a solution of 3-(3-methyl-1*H*-pyrazol-4-yl)-*N*-phenyl-1,2,4-thiadiazol-5-amine

(0.39 mmol, 0.10 mg) in THF (10 mL). After 30 minutes, methyl iodide (1.2 mmol, 73 µL) was added and the reaction mixture was stirred at room temperature for one hour. The reaction mixture was quenched with water at 0°C. The aqueous phase was extracted twice with DCM. The organic phase was washed with a sodium bisulfite solution, water and brine. Then the organic phase was dried over Na_2SO_4, was filtered and was concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel using cyclohexane/AcOEt (85:15) as eluent to yield 3-(1,3-dimethyl-1*H*-pyrazol-4-yl)-*N*-methyl-*N*-phenyl-1,2,4-thiadiazol-5-amine and 3-(1,5-dimethyl-1*H*-pyrazol-4-yl)-*N*-methyl-*N*-phenyl-1,2,4-thiadiazol-5-amine (0.32 mmol, 90 mg, 81%) as a colorless oil.

LC (Method LC-A): RT = 4.21 and 4.31min; MS *m/z* ES^+= 286.

EXAMPLE 5: 3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine 1 (Final compound 1-22) and 3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine monochlohydrate salt (Final compound 1.22a)

5.1: Ethyl 1-(cyclopropylmethyl)-1H-pyrazole-4-carboxylate (a1)

According to Scheme 4, Step 1a of the general methodology, K_2CO_3 (5.35 mmol, 740 mg) and cyclopropylmethylbromide (7.12 mmol, 962 mg) were added to a solution of ethyl 1-H-pyrazole-4-carboxylate (3.57 mmol, 500 mg) in acetone (5 mL). The reaction mixture was stirred at reflux for 8 hours. After cooling to room temperature, inorganics were filtered off and the filtrated was concentrated to dryness affording ethyl 1-(cyclopropylmethyl)-1H-pyrazole-4-carboxylate (3.40 mmol, 660 mg, 95%) as colorless oil.

LC (Method LC-B): RT = 1.26 min; MS *m/z* ES^+= 195

^1H NMR (300 MHz, $CDCl_3$) δ ppm: 8.01 (s, 1 H) 7.91 (s, 1 H) 4.31 (q, 2 H) 4.00 (d, 2 H) 1.36 (t, 3 H) 1.19 - 1.32 (m, 1 H) 0.63 - 0.76 (m, 2 H) 0.32 - 0.45 (m, 2 H).

The following compounds are synthetized according to the same method:

Cpd	IUPAC Name	Method LC-MS; RT (min)	(MH^+)
a2	Ethyl 1-(3-fluorobenzyl)-1H-pyrazole-4-carboxylate	LC-B; 1.41	249
a3	Ethyl 1-(2-morpholinoethyl)-1H-pyrazole-4-carboxylate	LC-B; 1.71	254
a4	Ethyl 1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carboxylate	LC-B; 1.23	223
a5	Ethyl 1-(cyclobutylmethyl)-1H-pyrazole-4-carboxylate	LC-B; 1.41	209
a6	Ethyl 1-((tetrahydrofuran-2-yl)methyl)-1H-pyrazole-4-carboxylate	LC-B; 1.06	225
a7	Ethyl 1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-pyrazole-4-carboxylate	LC-B; 1.11	239
a8	Ethyl 1-ethyl-1H-pyrazole-4-carboxylate	LC-B; 1.13	169
a9	Ethyl 1-propyl-1H-pyrazole-4-carboxylate	LC-D; 1.12	183
a10	Ethyl 1-(2-methoxyethyl)-1H-pyrazole-4-carboxylate	LC-B; 0.96	199
a11	Ethyl 1-cyclobutyl-1H-pyrazole-4-carboxylate	LC-B; 1.28	195
a12	Ethyl 3,5-dimethyl-1-propyl-1H-pyrazole-4-carboxylate	LC-B; 1.36	211
a13	Ethyl 1-(cyclopropylmethyl)-3,5-dimethyl-1H-pyrazole-4-carboxylate	LC-B; 1.40	223
a14	Ethyl 1-(cyclopropylmethyl)-3-(trifluoromethyl)-1H-pyrazole-4-carboxylate CP0264-120 (NMR)	LC-B; 1.59	263

Cpd	IUPAC Name	Method LC-MS; RT (min)	(MH^+)
a15	ethyl 1-propyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxylate	LC-B; 1.57	251
a16	Ethyl 1-(2,2,2-trifluoroethyl)-3-(trifluoromethyl)-1H-pyrazole-4-carboxylate	LC-C; 2.38	291

5.2 1-(Cyclopropylmethyl)-1H-pyrazole-4-carboximidamide hydrochloride (b1)

According to Scheme 4 Step 2 of the general methodology, trimethylaluminium, 2M solution in hexane (32.99 mmol, 16.5 mL), was added dropwise to a suspension of ammonium chloride (32.99 mmol, 1.75 g) in dry toluene (17 mL), under a nitrogen atmosphere, at 0°C. The reaction mixture was stirred at room temperature until no more evolution of gas was observed. After addition of ethyl 1-(cyclopropylmethyl)-1H-pyrazole-4-carboxylate (3.29 mmol, 640 mg), the reaction mixture was stirred at 95°C overnight. It was then cooled down to 0°C and MeOH was added under stirring. The solvent was removed and the residue was triturated with MeOH (100 mL) and filtered. The filtrate was concentrated and the crude was purified by silica gel flash chromatography (eluent: DCM/MeOH = 80:20) to yield 1-(cyclopropylmethyl)-1H-pyrazole-4-carboximidamide hydrochloride (3.26 mmol, 652 mg, 98%) as a white solid.

LC (Method LC-B): RT = 0.64 min; MS *m/z* ES^+= 165.

^1H NMR (300 MHz, DMSO-d_6) δ ppm: 8.92 (br. s., 3 H) 8.72 (s, 1 H) 8.24 (d, 1 H) 4.06 (d, 2 H) 1.14 - 1.34 (m, 1 H) 0.53 - 0.65 (m, 2 H) 0.34 - 0.44 (m, 2 H).

The following compounds are synthetized according to the same method:

Cpd	IUPAC Name	Method LC-MS; RT (min)	(MH^+)
b2	1-(3-Fluorobenzyl)-1H-pyrazole-4-carboximidamide hydrochloride	LC-B; 0.85	219

Cpd	IUPAC Name	Method LC-MS; RT (min)	(MH^+)
b3	1-(2-Morpholinoethyl)-1H-pyrazole-4-carboximidamide hydrochloride	LC-D; 0.35	224
b4	1-(2,2,2-Trifluoroethyl)-1H-pyrazole-4-carboximidamide hydrochloride	LC-B; 0.45	193
b5	1-(Cyclobutylmethyl)-1H-pyrazole-4-carboximidamide hydrochloride	LC-B; 0.79	179
b6	1-((Tetrahydrofuran-2-yl)methyl)-1H-pyrazole-4-carboximidamide hydrochloride	LC-B; 0.57	195
b7	1-((Tetrahydro-2H-pyran-4-yl)methyl)-1H-pyrazole-4-carboximidamide hydrochloride	LC-B; 0.57	209
b8	1-Ethyl-1H-pyrazole-4-carboximidamide hydrochloride	LC-C; 0.36	139
b9	1-Propyl-1H-pyrazole-4-carboximidamide hydrochloride	LC-B; 0.30	153
b10	1-(2-Methoxyethyl)-1H-pyrazole-4-carboximidamide hydrochloride	LC-B; 0.38	169
b11	1-Cyclobutyl-1H-pyrazole-4-carboximidamide hydrochloride	LC-B; 0.63	165
b12	3,5-Dimethyl-1-propyl-1H-pyrazole-4-carboximidamide hydrochloride	LC-B; 0.49	181
b13	1-(Cyclopropylmethyl)-3,5-dimethyl-1H-pyrazole-4-carboximidamide hydrochloride	LC-B; 1.59	263
b14	1-(Cyclopropylmethyl)-3-(trifluoromethyl)-1H-pyrazole-4-carboximidamide hydrochloride	LC-B; 0.88	233

Cpd	IUPAC Name	Method LC-MS; RT (min)	(MH^+)
b15	1-Propyl-3-(trifluoromethyl)-1H-pyrazole-4-carboximidamide hydrochloride	LC-B; 0.88	221
b16	1-(2,2,2-Trifluoroethyl)-3-(trifluoromethyl)-1H-pyrazole-4-carboximidamide hydrochloride	LC-C; 0.93	261

5.3 Synthesis of isothiocyanato derivatives

5.3.1 *6-Morpholinopyridin-2-amine* (c1)

A mixture of 6-bromopyridine-2-amine (5.20 mmol, 0.90 g) and morpholine (57.39 mmol, 5 mL) was heated at 150°C for 4 hours under microwave irradiation. AcOEt was added and the organic phase was washed with $NaHCO_3$, water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 6-morpholinopyridin-2-amine (5.20 mmol, 1.06 g, 100%) as a light brown solid. The crude product was used in the next step without further purification.
LC (Method LC-B): RT = 0.29 min; MS *m/z* ES^+= 180.

5.3.2 *5-Morpholinopyridin-2-amine* (c2)

A mixture of 5-bromo-2-nitropyridine (0.49 mmol, 100 mg) and morpholine (11.48 mmol, 1 mL) was heated at 100°C for 30 minutes under microwave irradiation. After evaporation of the solvent, the crude mixture was purified on a silica gel cartridge (2g) eluted a first time with petroleum ether/AcOEt (90:10), then with DCM to afford 4-(6-nitropyridin-3-yl)morpholine (0.43 mmol, 89 mg, 88%) as a yellow solid.
LC (Method LC-C): RT = 1.25 min; MS *m/z* ES^+= 210.
4-(6-Nitropyridin-3-yl)morpholine (0.40 mmol, 83 mg) was dissolved in AcOEt (30 mL) and MeOH (2 mL). Palladium on activated charcoal 10% (20 mg) was added and the reaction mixture was hydrogenated on a Parr apparatus (15 psi) for 1.5 hours at

room temperature. The reaction mixture was filtered to remove the catalyst and after evaporation of the solvent 5-morpholinopyridin-2-amine (0.40 mmol, 72 mg, 100%) was recovered as a pale brown solid. The crude product was used in the next step without purification.

LC (Method LC-D): RT = 0.43 min; MS *m/z* ES^+= 180.

^1H NMR (300 MHz, DMSO-d_6) δ ppm: 7.60 (d, 1 H) 7.16 (dd, 1 H) 6.41 (d, 1 H) 5.37 (s, 2 H) 3.64 - 3.77 (m, 4 H) 2.84 - 2.95 (m, 4 H).

5.3.3 *6-Cyclobutoxypyridin-2-amine* (c3)

Sodium hydride (3.80 mmol, 150 mg) was added portionwise to a solution of cyclobutanol (3.46mmmol, 0.27 mL) in acetonitrile and the reaction mixture was stirred 1 hour at room temperature. 6-Bromopyridine-2-amine (1.73 mmol, 0.30 g) was added and the reaction mixture was heated at 130°C for 3 hours under microwave irradiation. After evaporation of the solvent, water was added and the aqueous phase was extracted with AcOEt. The organic phase was washed with water, brine and dried over Na_2SO_4. The organic solvent was filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel using petroleum ether/AcOEt (80:20) as eluent affording 6-cyclobutoxypyridin-2-amine (0.85 mmol, 0.14 g, 49%) as a yellow oil.

LC (Method LC-B): RT = 0.83 min; MS *m/z* ES^+= 165.

5.3.4 *2-Isothiocyanatopyridine* (*or its dimer 2-(pyridin-2-yl)-4-(pyridin-2-ylimino)-1,2-thiazetidine-3-thione*) d1 (Method A)

1,1'-Thiocarbonyldimidazole solution (5.84 mmol, 1.04 g) in dichloromethane (10 mL) was added dropwise to 2-amino-pyridine (5.31 mmol, 0.50g) in dichloromethane (10 mL) at 0°C under nitrogen. The reaction mixture was warmed to room temperature and stirred for 5 hours. The reaction mixture was concentrated and purified on a silica gel cartridge (Isolute SPE column 10G 25mL; eluent: petroleum ether/AcOEt = 100:0 to 90:10) affording 2-isothiocyanatopyridine (1.76 mmol, 0.24 g, 33 %) as yellow oil;

LC (Method LC-D): RT = 1.17 min; MS *m/z* ES^+= 137.

Upon standing *in vacuo* 48 hours the product converted quantitatively into 2-(pyridin-2-yl)-4-(pyridin-2-ylimino)-1,2-thiazetidine-3-thione appearing as an orange solid.
LC (Method LC-D): RT = 0.92 min; MS *m/z* ES^+= 273.
^1H NMR (300 MHz, DMSO-d_6) δ ppm: 9.16 - 9.32 (m, 1 H) 8.51 - 8.63 (m, 1 H) 8.03 - 8.12 (m, 1 H) 7.95 - 8.03 (m, 1 H) 7.41 - 7.49 (m, 2 H) 7.33 - 7.40 (m, 1 H) 7.25 (td, 1 H)

5.3.5 *2-Isothiocyanato-6-methylpyridine* d2 (Method A)
1,1'-Thiocarbonyldimidazole solution (3.70 mmol, 0.66 g) in DCM (5 mL) was added dropwise to 2-amino-6-methylpyridine (3.70 mmol, 0.40 g) in DCM (8 mL) at 0°C under a nitrogen atmosphere. The reaction mixture was warmed to room temperature and stirred for 1 hour. The reaction mixture was concentrated and purified by flash chromatography over silica gel using petroleum ether/AcOEt (90:10 to 80:20) as eluent affording 2-isothiocyanato-6-methylpyridine (1.21 mmol, 0.18 mg, 33 %) as pale yellow oil;
LC (Method LC-B): RT =1.40 min; MS *m/z* ES^+= 151.
^1H NMR (300 MHz, $CDCl_3$) δ ppm: 7.60 (dd, 1 H) 7.07 (d, 1 H) 6.96 (d, 1 H) 2.53 (s, 3 H).

The following compounds are synthetized according to the same method:

Cpd	IUPAC Name	Method LC-MS; RT (min)	(MH^+)	From amine c or [CAS]
d3	5-Isothiocyanato-2-methoxypyridine	LC-B; 1.57	167	[27231-36-3]
d4	3-Isothiocyanato-2-methoxypyridine	LC-B; 1.59	167	[20265-38-7]
d5	5-Chloro-2-isothiocyanatopyridine	LC-B; 1.58	171	[1072-98-6]

5.3.6 *2-Isothiocyanato-6-ethylpyridine* d6 (Method B) TEA (1.50 mmol, 0.21 ml) and thiophosgene (0.52 mmol, 0.04 mL) were added to a solution of 2-amino-6-ethylpyridine (0.50 mmol, 60 mg) in THF (5 mL). The reaction mixture was stirred 1 hour at room temperature under a nitrogen atmosphere. After evaporation of the solvent 2-isothiocyanato-6-ethylpyridine was recovered as a brown solid and used in the next step without further purification.

LC (Method LC-B): RT =1.62 min; MS *m/z* ES^+= 165.

The following compounds are synthetized according to the same method:

Cpd	IUPAC Name	Method LC-MS; RT (min)	(MH^+)	From amine c or [CAS]
d7	2-Isothiocyanato-6-(trifluoromethyl)pyridine	LC-C; 2.59	205	[34486-24-3]
d8	2-Isothiocyanato-4-(trifluoromethyl)pyridine	LC-B; 1.65	205	[106447-97-62]
d9	2-Isothiocyanato-3-(trifluoromethyl)pyridine	LC-C; 2.52	205	[183610-70-03]
d10	2-Fluoro-6-isothiocyanatopyridine	LC-B; 1.48	155	[1597-32-6]
d11	5-Fluoro-2-isothiocyanatopyridine	LC-D; 1.30	155	[21717-96-4]
d12	3,5-Difluoro-2-isothiocyanatopyridine	LC-B; 1.53	173	[732306-31-9]
d13	2-Methyl-4-isothiocyanatopyridine	LC-B; 0.60	151	[18437-58-6]
d14	2-Isothiocyanatoquinoline	LC-B; 1.62	187	[580-22-3]
d15	6-Isothiocyanatonicotinonitrile	LC-D; 1.24;	162	[4214-73-7]
d16	2-Isothiocyanato-6-methoxypyridine	LC-B; 1.63	167	[17920-35-3]
d17	4-(6-Isothiocyanatopyridin-2-	LC-B; 1.61	222	c1

Cpd	IUPAC Name	Method LC-MS; RT (min)	(MH^+)	From amine c or [CAS]
	yl)morpholine			
d18	4-(6-Isothiocyanatopyridin-3-yl)morpholine	LC-D; 1.23	222.2	c2
d19	Methyl 6-isothiocyanatonicotinate	LC-D; 1.35	195.1	[36052-24-1]
d20	2-Cyclobutoxy-6-isothiocyanatopyridine	LC-B; 1.97	207.2	c3

5.4 3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine 1 (Final compound 1-22) and 3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine monochlohydrate salt (Final compound 1.22a)

According to Scheme 4 Step 3 of the general methodology, 2-(pyridin-2-yl)-4-(pyridin-2-ylimino)-1,2-thiazetidine-3-thione (1.74 mmol, 475 mg) and DBU (5.237 mmol, 797 mg) were added to a solution of 1-(cyclopropylmethyl)-1H-pyrazole-4-carboximidamide hydrochloride (1.74 mmol, 350 mg) in dry DMF (2.5 mL). The reaction mixture was stirred at room temperature for 15 minutes. Di-*tert*-butylazodicarboxylate (1.92 mmol, 442 mg) was added and the reaction mixture was stirred at room temperature for 15 minutes. Water was added and the aqueous phase was extracted with AcOEt. The organic phase was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was triturated twice in acetonitrile affording 3-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine (0.705 mmol, 210 mg, 40%) as a light brown powder.

LC (Method LC-E): RT = 1.89 min; MS *m/z* ES+= 299.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 12.05 (br. s., 1 H) 8.42 (ddd, 1 H) 8.25 (d, 1 H) 7.89 (d, 1 H) 7.77 - 7.86 (m, 1 H) 7.12 - 7.19 (m, 1 H) 7.02 - 7.09 (m, 1 H) 4.04 (d, 2 H) 1.20 - 1.38 (m, 1 H) 0.51 - 0.61 (m, 2 H) 0.34 - 0.45 (m, 2 H).

Melting point: 237-238 °C.

Preparation of 5.4 3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine 1 (Final compound 1-22a)

To a solution of 3-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine (0.134 mmol, 40 mg) in dioxane (8 mL), a solution of HCl in dioxane (4N, 0.4 mmol, 0.1 mL) was added and the reaction mixture was stirred 30 minutes at room temperature. After evaporation of the solvent, the residue was triturated in AcOEt affording 3-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine hydrochloride (0.107 mmol, 36 mg, 80%) as a pale yellow powder.

LC (Method LC-E): RT = 1.80 min; MS *m/z* ES+= 299.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 12.22 (s, 1 H), 8.39 - 8.45 (m, 1 H), 8.25 (d, 1 H), 7.89 (d, 1 H), 7.77 - 7.86 (m, 1 H), 7.12 - 7.19 (m, 1 H), 7.02 - 7.10 (m, 1 H), 4.04 (d, 2 H), 1.19 - 1.39 (m, 1 H), 0.51 - 0.60 (m, 2 H), 0.35 - 0.44 (m, 2 H).

Melting point: 222-224 °C.

Elemental analysis confirm formation of monochlorhydrate salt.

The following compounds are synthetized according to the same method used for compound **1.22**:

Cpd	IUPAC Name	Method LC-MS; RT (min)	(MH^+)	From b	From d or [CAS]
1-14	3-(1-Ethyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine	LC-E; 1.65	273	b8	d1
1-15	3-(1-Ethyl-1H-pyrazol-4-yl)-N-(6-methoxypyridin-2-yl)-	LC-E; 1.82	303	b8	d16

Cpd	IUPAC Name	Method LC-MS; RT (min)	(MH^+)	From b	From d or [CAS]
	1,2,4-thiadiazol-5-amine				
1-16	3-(1-Ethyl-1H-pyrazol-4-yl)-N-(6-morpholinopyridin-2-yl)-1,2,4-thiadiazol-5-amine	LC-E; 1.74	358	b8	d17
1-18	3-(1-Propyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine	LC-E; 1.76	287	b9	d1
1-19	3-(1-(3-Fluorobenzyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.15	353	b2	d1
1-20	3-(1-(3-Fluorobenzyl)-1H-pyrazol-4-yl)-N-phenyl-1,2,4-thiadiazol-5-amine	LC-E; 2.40	352	b2	[103-72-0]
1-21	N-(Pyridin-2-yl)-3-(1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	LC-E; 1.73	343	b7	d1
1-23	3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(6-methylpyridin-2-yl)-1,2,4-thiadiazol-5-amine	LC-F; 3.06	313	b1	d2
1-24	3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(6-ethylpyridin-2-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.20	327	b1	d6

Cpd	IUPAC Name	Method LC-MS; RT (min)	(MH^+)	From b	From d or [CAS]
1-25	3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(6-fluoropyridin-2-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.04	317	b1	d10
1-26	3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(5-fluoropyridin-2-yl)-1,2,4-thiadiazol-5-amine	LC-E; 1.94	317	b1	d11
1-27	3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(6-methoxypyridin-2-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.04	329	b1	d16
1-28	N-(6-Cyclobutoxypyridin-2-yl)-3-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.37	369	b1	d20
1-29	3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(6-morpholinopyridin-2-yl)-1,2,4-thiadiazol-5-amine	LC-E; 1.94	384	b1	d17
1-30	3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(5-morpholinopyridin-2-yl)-1,2,4-thiadiazol-5-amine	LC-E; 1.71	384	b1	d18

Cpd	IUPAC Name	Method LC-MS; RT (min)	(MH^+)	From b	From d or [CAS]
1-31	3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(6-(trifluoromethyl)pyridin-2-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.21	367	b1	d7
1-32	N-(5-Chloropyridin-2-yl)-3-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.15	333	b1	d5
1-36	3-(1-(Cyclobutylmethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.06	313	b5	d1
1-37	3-(1-(2-Morpholinoethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine	LC-E; 1.36	358	b3	d1
1-38	N-(Pyridin-2-yl)-3-(1-((tetrahydrofuran-2-yl)methyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	LC-E; 1.66	329	b6	d1
1-39	N-(Pyridin-2-yl)-3-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	LC-E; 1.96	327	b4	d1
1-40	3-(1-(2-Methoxyethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine	LC-E; 1.54	303	b10	d1

Cpd	IUPAC Name	Method LC-MS; RT (min)	(MH^+)	From b	From d or [CAS]
1-42	3-(1-Cyclobutyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine	LC-E; 1.86	299	b11	d1
1-46	3-(1-Propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.44	355	b15	d1
1-47	N-(6-Methylpyridin-2-yl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.61	369	b15	d2
1-48	N-(6-Methoxypyridin-3-yl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.34	385	b15	d3
1-49	N-(2-Methoxypyridin-3-yl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.60	385	b15	d4
1-50	N-(5-Chloropyridin-2-yl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.77	389	b15	d5
1-51	3-(1-Propyl-3-	LC-E; 2.81	422	b15	d8

Cpd	IUPAC Name	Method LC-MS; RT (min)	(MH^+)	From b	From d or [CAS]
	(trifluoromethyl)-1H-pyrazol-4-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)-1,2,4-thiadiazol-5-amine				
1-52	N-(3,5-Difluoropyridin-2-yl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	LC-F; 3.83	391	b15	d12
1-53	3-(1-Propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-N-(quinolin-2-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.82	405	b15	d14
1-54	N-(2-Methylpyridin-4-yl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	LC-E; 1.69	369	b15	d13
1-55	N-(2-Fluorophenyl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.71	372	b15	[38985-64-7]
1-56	N-(2,5-Difluorophenyl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.75	390	b15	[206559-57-1]

Cpd	IUPAC Name	Method LC-MS; RT (min)	(MH^+)	From b	From d or [CAS]
1-57	N-(Benzo[d][1,3]dioxol-5-yl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.55	398	b15	[113504-93-1]
1-58	N-(4-Morpholinophenyl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.06	439	b15	[51317-66-9]
1-59	N-(3-Methoxyphenyl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.67	384	b15	[3125-64-2]
1-60	3-(1-Propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-N-(3-(trifluoromethyl)phenyl)-1,2,4-thiadiazol-5-amine	LC-E; 2.91	421	b15	[1840-19-3]
1-61	N-(4-Chlorophenyl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.91	388	b15	[2131-55-7]
1-62	3-(1-(Cyclopropylmethyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine	LC-E; 3.18	367	b14	d1

Cpd	IUPAC Name	Method LC-MS; RT (min)	(MH^+)	From b	From d or [CAS]
1-63	N-(Pyridin-2-yl)-3-(1-(2,2,2-trifluoroethyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.50	395	b16	d1
1-64	3-(3,5-Dimethyl-1-propyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.06	315	b12	d1
1-65	3-(1-(Cyclopropylmethyl)-3,5-dimethyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.03	327	b13	d1
1-66	3-(1-(Cyclopropylmethyl)-3,5-dimethyl-1H-pyrazol-4-yl)-N-(6-methylpyridin-2-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.16	341	b13	d2

EXAMPLE 6: 3-(1-Ethyl-3-methyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine (Final compound 1-17)

6.1: Methyl 1-ethyl-3-methyl-1H-pyrazole-4-carboxylate a17

According to Scheme 4 Step 1b of the general methodology, a solution of 1-ethyl-3-methyl-1H-pyrazole-4-carboxylic acid (3.24 mmol, 0.50 g) and sulphuric acid 96% (0.5 mL) in methanol (5 mL) was heated at 70°C for 48 hours. After evaporation of the solvent, AcOEt was added and the organic phase was washed with a saturated solution of $NaHCO_3$, water and brine, dried over Na_2SO_4, filtered and concentrated under

reduced pressure affording methyl 1-ethyl-3-methyl-1H-pyrazole-4-carboxylate (1.78 mmol, 0.30 g, 55%) as a pale yellow oil.
The crude product was used without further purification.
LC (Method LC-B): RT = 1.07 min; MS *m/z* ES^+= 169.

The following compounds are synthesized according to the same method (for compound a19 ethanol was used instead of methanol):

Cpd	Name	Method LC-MS; RT (min)	(MH^+)
a18	Methyl 3-methyl-1-propyl-1H-pyrazole-4-carboxylate	LC-B; 1.22	183
a19	Ethyl 1-(4-fluorophenyl)-5-methyl-1H-pyrazole-4-carboxylate	LC-B; 1.49	249

6.2 1-Ethyl-3-methyl-1H-pyrazole-4-carboximidamide hydrochloride b17
According to Scheme 4 Step 2 of the general methodology, trimethylaluminium, 2M solution in toluene (17.83 mmol, 8.90 mL), was added dropwise to a suspension of ammonium chloride (17.83 mmol, 0.954 g) in dry toluene (15 mL), under a nitrogen atmosphere, at 0°C. The reaction mixture was stirred at room temperature until no more evolution of gas was observed. After addition of methyl 1-ethyl-3-methyl-1H-pyrazole-4-carboxylate (1.783 mmol, 0.30 g), the reaction mixture was stirred at 90°C overnight. The reaction mixture was then cooled down to 0°C and MeOH was added under stirring. The solvent was removed and the residue was tritured with MeOH (50 mL) and filtered. The filtrate was concentrated and the crude was purified by flash chromatography over silica gel, using DCM/MeOH (80:20) as eluent, to yield 1-ethyl-3-methyl-1H-pyrazole-4-carboximidamide hydrochloride (1.43 mmol, 270 mg, 80%) as a white solid.
LC (Method LC-B): RT = 0.40 min; MS *m/z* ES^+= 153.

The following compounds were synthesized according to the same method:

Cpd	IUPAC Name	Method LC-MS; RT (min)	(MH^+)
b18	3-Methyl-1-propyl-1H-pyrazole-4-carboximidamide hydrochloride	LC-B; 0.32	167
b19	1-(4-Fluorophenyl)-5-methyl-1H-pyrazole-4-carboximidamide hydrochloride	LC-B; 0.80	219

6.3 3-(1-Ethyl-3-methyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine (Final compound 1-17)

According to Scheme 4 Step 3 of the general methodology, 2-(pyridin-2-yl)-4-(pyridin-2-ylimino)-1,2-thiazetidine-3-thione (0.53 mmol, 145 mg) and DBU (1.59 mmol, 242 mg) were added to a solution of 1-ethyl-3-methyl-1H-pyrazole-4-carboximidamide hydrochloride (0.53 mmol, 100 mg) in dry DMF (1 mL) and the reaction mixture was stirred at room temperature for 15 minutes. Di-tert-butyl diazene-1,2-dicarboxylate (0.583 mmol, 135 mg) was added and the reaction mixture was stirred at room temperature for 30 minutes. Water was added and the aqueous phase was extracted with AcOEt. The organic phase was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel using DCM/MeOH/NH_4OH (32%) (95:5:0.5) as eluent and then the solid was triturated in di-isopropyl ether affording 3-(1-ethyl-3-methyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine (0.157 mmol, 45 mg, 30%) as a light brown powder.

LC (Method LC-E): RT = 1.70 min; MS *m/z* ES+= 287.

^1H NMR (300 MHz, $CDCl_3$)δ ppm: 9.93 (s, 1 H) 8.46 (ddd, 1 H) 7.92 (s, 1 H) 7.60 (ddd, 1 H) 6.93 - 7.03 (m, 1 H) 6.71 (dt, 1 H) 4.11 (q, 2 H) 2.66 (s, 3 H) 1.45 (t, 3 H).

Melting point: 203-205 °C.

The following compounds are synthesized according to the same method:

Cpd	IUPAC Name	Method LC-MS; RT (min)	(MH^+)	From b	From d or [CAS]
1-44	3-(1-(4-Fluorophenyl)-5-methyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.37	353	b19	d1
1-45	3-(1-(4-Fluorophenyl)-5-methyl-1H-pyrazol-4-yl)-N-phenyl-1,2,4-thiadiazol-5-amine	LC-E; 2.53	352	b19	[103-72-0]
1-67	3-(3-Methyl-1-propyl-1H-pyrazol-4-yl)-N-(6-methylpyridin-2-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.17	315.14	b18	d2
1-68	N-(6-Ethylpyridin-2-yl)-3-(3-methyl-1-propyl-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.26	329.14	b18	d6
1-69	3-(3-Methyl-1-propyl-1H-pyrazol-4-yl)-N-(6-(trifluoromethyl)pyridin-2-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.33	369	b18	d7
1-70	3-(3-Methyl-1-propyl-1H-pyrazol-4-yl)-N-(3-(trifluoromethyl)pyridin-2-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.27	369	b18	d9
1-71	N-(5-Chloropyridin-2-yl)-3-(3-methyl-1-propyl-1H-pyrazol-4-yl)-1,2,4-	LC-E; 2.24	335	b18	d5

Cpd	IUPAC Name	Method LC-MS; RT (min)	(MH^+)	From b	From d or [CAS]
	thiadiazol-5-amine				
1-72	N-(5-Fluoropyridin-2-yl)-3-(3-methyl-1-propyl-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.07	319	b18	d11
1-73	6-(3-(3-methyl-1-propyl-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-ylamino)nicotinonitrile	LC-E; 1.94	326	b18	d15
1-74	3-(3-Methyl-1-propyl-1H-pyrazol-4-yl)-N-(6-morpholinopyridin-2-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.02	386	b18	d17
1-75	N-(6-Methoxypyridin-2-yl)-3-(3-methyl-1-propyl-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.14	331	b18	d16
1-76	N-(6-Fluoropyridin-2-yl)-3-(3-methyl-1-propyl-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	LC-E; 2.12	319	b18	d10

EXAMPLE 7: 3-(1-(3-Fluoro-4-methoxyphenyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine (Final compound 1-43)

7.1: Ethyl 1-(3-fluoro-4-methoxyphenyl)-1H-pyrazole-4-carboxylate a20

According to Scheme 4 Step 1a of the general methodology, copper iodide (0.214 mmol, 41 mg), 1-10-phenanthroline (0.428 mmol, 77 mg) and K_2CO_3 (10.71 mmol, 1.48 g) were added to a solution of ethyl 1H-pyrazole-4-carboxylate (4.28 mmol, 600 mg) and 4-bromo-2-fluoro-1-methoxybenzene (6.43 mmol, 0.83 mL) in dry dioxane (9 mL). The reaction mixture was heated at 150°C for 5h under microwave irradiation. The mixture was filtered through a Celite® pad. After evaporation of the solvent the crude product was purified on a silica gel cartridge eluted with petroleum ether/AcOEt (100:0 to 90:10) as solvent affording ethyl 1-(3-fluoro-4-methoxyphenyl)-1H-pyrazole-4-carboxylate (0.728 mmol, 191 mg, 17%) as a white solid.
LC (Method LC-C): RT = 2.31 min; MS *m/z* ES^+= 265.

7.2: 1-(3-Fluoro-4-methoxyphenyl)-1H-pyrazole-4-carboximidamidehydrochloride b20

According to Scheme 4 Step 2 of the general methodology, trimethylaluminium, 2M solution in toluene (7.23 mmol, 3.62 mL), was added dropwise to a suspension of ammonium chloride (7.23 mmol, 383 mg) in dry toluene (10 mL), under a nitrogen atmosphere, at 0°C. The reaction mixture was stirred at room temperature until no more evolution of gas was observed. After addition of ethyl 1-(3-fluoro-4-methoxyphenyl)-1H-pyrazole-4-carboxylate (0.723 mmol, 191 mg), the reaction mixture was stirred at 90°C for 5 hours. The reaction mixture was then cooled down to 0°C and MeOH was added under stirring. The solvent was removed and the residue was tritured with MeOH (50 mL) and filtered. The filtrate was concentrated and the crude obtained was purified on a silica gel cartridge eluted with DCM/MeOH (90:10 to 80:20) affording 1-(3-fluoro-4-methoxyphenyl)-1H-pyrazole-4-carboximidamide hydrochloride (0.646 mmol,175 mg, 90%) as a white solid.
LC (Method LC-C): RT = 1.22 min; MS *m/z* ES^+= 235

7.3: 3-(1-(3-Fluoro-4-methoxyphenyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine (Final compound 1-43)

According to Scheme 4 Step 3 of the general methodology, 2-(pyridin-2-yl)-4-(pyridin-2-ylimino)-1,2-thiazetidine-3-thione (0.648 mmol, 176 mg) and DBU (1.296 mmol, 194 µL) were added to a solution of 1-(3-fluoro-4-methoxyphenyl)-1H-pyrazole-4-carboximidamide hydrochloride b20 (0.648 mmol, 175 mg) in dry DCM (10 mL) and the reaction mixture was stirred at room temperature for 15 minutes. Di-*tert*-butylazodicarboxylate (0.713 mmol, 164 mg) was added and the reaction mixture was stirred at room temperature for 1 hour. After evaporation of the solvent, water was added and the aqueous phase was extracted with AcOEt. The organic phase was washed with water and brine, dried over Na_2SO_4, filtered and was concentrated under reduced pressure. The crude product was triturated in acetonitrile, isopropanol and then in methanol affording 3-(1-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine (0.312 mmol, 115 mg, 48%) as a pale pink powder.
LC (Method LC-E): RT = 2.17 min; MS *m/z* ES+= 369.
^{1}H NMR (300 MHz, DMSO-d_6) δ ppm:12.15 (br. s., 1 H) 8.91 (s, 1 H) 8.44 (ddd, 1 H) 8.17 (s, 1 H) 7.80 - 7.93 (m, 2 H) 7.68 - 7.78 (m, 1 H) 7.32 (dd, 1 H) 7.15 - 7.23 (m, 1 H) 7.00 - 7.12 (m, 1 H) 3.90 (s, 3 H).

EXAMPLE 8: 6-(3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-ylamino)-nicotinonitrile (Final compound 1-33)

8.1: 5-Chloro-3-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazole e1 from b1**:** According to Scheme 5 Step 1 of the general methodology, trichloromethanesulfenyl chloride (2.00 mmol, 220 µL) was added under vigorous stirring to a solution of 1-(cyclopropylmethyl)-1H-pyrazole-4-carboximidamide hydrochloride (2.00 mmol, 400 mg) in water (12 mL) cooled at 0°C. A solution of NaOH (9.40 mmol, 376 mg) in water (8 mL) was added and the reaction mixture was stirred 1 hour at room temperature. DCM was added and the organic phase was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified on a silica gel cartridge eluted with petroleum ether/AcOEt (100:0

to 90:10) as solvent affording 5-chloro-3-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazole (0.436 mmol, 105 mg, 22%).

LC (Method LC-D): RT = 1.31 min; MS *m/z* ES^+= 241.

^1H NMR (300 MHz, DMSO-d_6) δ ppm: 8.45 (d, 1 H) 8.00 (d, 1 H) 4.04 (d, 2 H) 1.21 - 1.37 (m, 1 H) 0.47 - 0.60 (m, 2 H) 0.35 - 0.47 (m, 2 H).

8.2: 6-(3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-ylamino)-nicotinonitrile (Final compound 1-33)

According to Scheme 5 Step 2 of the general methodology, a mixture of 5-chloro-3-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazole (0.22 mmol, 54 mg), 6-aminonicotinonitrile (0.44 mmol, 53 mg) and sodium *tert*-butoxide (0.33 mmol, 32 mg) in dioxane (3 mL) was heated under reflux overnight. Sodium tert-butoxide (0.11 mmol, 12 mg) was added and the reaction mixture was refluxed for other 5 hours. After cooling at room temperature the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography over silica gel using DCM/MeOH (95:5) as eluent. The resulting solid was further purified by trituration in MeOH affording 6-(3-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-ylamino)-nicotinonitrile (0.043 mmol, 14 mg, 20%).

LC (Method LC-E): RT = 1.89 min; MS *m/z* ES+= 324.

^1H NMR (300 MHz, DMSO-d_6) δ ppm: 12.77 (br. s., 1 H) 8.91 (dd, 1 H) 8.27 (s, 1 H) 8.20 (dd, 1 H) 7.91 (s, 1 H) 7.23 (d, 1 H) 4.04 (d, 2 H) 1.19 - 1.37 (m, 1 H) 0.50 - 0.60 (m, 2 H) 0.35 - 0.44 (m, 2 H).

The following compound is prepared according to the same method:

Cpd	IUPAC Name	Method LC-MS; RT (min)	(MH^+)	From e	From amine or [CAS]
1-34	3-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(pyrazin-2-	LC-E; 1.64	300	e1	[5049-61-6]

Cpd	IUPAC Name	Method LC-MS; RT (min)	(MH^+)	From e	From amine or [CAS]
	yl)-1,2,4-thiadiazol-5-amine				

EXAMPLE 9: 2-(4-(5-(Pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)-1H-pyrazol-1-yl)ethanol (Final compound 1-41)

9.1: Ethyl 1-(2-(benzyloxy)ethyl)-1H-pyrazole-4-carboxylate a21

According to Scheme 4 Step 1a of the general methodology, a mixture of ethyl 1H-pyrazole-4-carboxylate (3.57 mmol, 500 mg), ((2-bromoethoxy)methyl)benzene (5.31 mmol, 1.14 g) and K_2CO_3 (5.355 mmol, 739 mg) in acetone (20 mL) was heated under reflux for 24 hours. After cooling to room temperature the mixture was filtered. After evaporation of the solvent under reduced pressure, the crude was purified by flash chromatography over silica gel using petroleum ether/AcOEt (90:10 to 80:20) as eluent affording ethyl 1-(2-(benzyloxy)ethyl)-1H-pyrazole-4-carboxylate (2.916 mmol, 800 mg, 82%) as a colourless oil.

LC (Method LC-B): RT = 1.40 min; MS *m/z* ES^+= 275.

9.2: 1-(2-(Benzyloxy)ethyl)-1H-pyrazole-4-carboximidamide hydrochloride b21

According to Scheme 4 Step 2 of the general methodology, trimethylaluminium, 2M solution in toluene (18.20 mmol, 9.15 mL), was added dropwise to a suspension of ammonium chloride (18.20 mmol, 975 mg) in dry toluene (15 mL), under a nitrogen atmosphere, at 0°C. The reaction mixture was stirred at room temperature until no more evolution of gas was observed. After addition of ethyl 1-(2-(benzyloxy)ethyl)-1H-pyrazole-4-carboxylate (1.82 mmol, 500 mg), the reaction mixture was stirred at 95°C overnight. The reaction mixture was then cooled down to 0°C and MeOH was added under stirring. The solvent was removed and the residue was tritured with MeOH (100 mL) and filtered. The filtrate was concentrated and the crude obtained was purified by

flash chromatography over silica gel using DCM/MeOH (80:20) as eluent affording 1-(2-(benzyloxy)ethyl)-1H-pyrazole-4-carboximidamide hydrochloride (1.57 mmol, 440mg, 86%) as a pale yellow oil.
LC (Method LC-B): RT = 0.87 min; MS *m/z* ES^+= 245.

9.3: 3-(1-(2-(Benzyloxy)ethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine f1
According to Scheme 4 Step 3 of the general methodology, 2-(pyridin-2-yl)-4-(pyridin-2-ylimino)-1,2-thiazetidine-3-thione (0.28 mmol, 75 mg) and DBU (0.57 mmol, 85 µL) were added to a solution of 1-(2-(benzyloxy)ethyl)-1H-pyrazole-4-carboximidamide hydrochloride (0.28 mmol, 80 mg) in dry DMF (5 mL) and the reaction mixture was stirred at room temperature for 20 minutes. Di-*tert*-butylazodicarboxylate (0.31 mmol, 70 mg) was added and the reaction mixture was stirred at room temperature for 20 minutes. Water was added and the aqueous phase was extracted with AcOEt. The organic phase was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was tritured in acetonitrile affording 3-(1-(2-(benzyloxy)ethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine (0.172 mmol, 65 mg, 61%) as a pale brown solid.
LC (Method LC-B): RT = 1.43 min; MS *m/z* ES^+= 379.

9.4: 2-(4-(5-(Pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)-1H-pyrazol-1-yl)ethanol (Final compound 1-41)
According to Scheme 4 Step 4a of the general methodology, 3-(1-(2(benzyloxy)ethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine (0.052 mmol, 20mg) was dissolved in DCM (4 mL) and TMSBr (0.068 mmol, 9 µl) was added in a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 72 hours with regular addition of TMSBr in portions of 9 µL until the total amount of (0.68 mmol, 90 µl) was reached. The reaction mixture was diluted with DCM and washed with water. The organic layer was separated, dried over Na_2SO_4 and concentrated. The crude was purified by silica gel flash chromatography (eluent: DCM/MeOH = 95:5) to yield 1- 2-

(4-(5-(pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)-1H-pyrazol-1-yl)ethanol (0.035 mmol, 10 mg, 67%) as a beige solid.

LC (Method LC-E): RT = 1.40 min; MS *m/z* ES+= 289.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 12.19 (s, 1 H), 8.35 - 8.48 (m, 1 H), 8.19 (s, 1 H), 7.89 (s, 1 H), 7.76 - 7.86 (m, 1 H), 7.10 - 7.20 (m, 1 H), 6.98 - 7.10 (m, 1 H), 4.21 (t, 2 H), 3.71 - 3.82 (m, 3 H).

EXAMPLE 10: 6-(3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-ylamino)nicotinamide (Final compound 1-35)

According to Scheme 4 Step 3 of the general methodology, methyl 6-(3-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-ylamino) nicotinate was prepared following the procedure described in Example 5 starting from (cyclopropylmethyl)-1H-pyrazole-4-carboximidamide hydrochloride (b1) and methyl 6-isothiocyanatonicotinate (d19) (LC (Method LC-D): RT = 1.25 min; MS *m/z* ES+= 357.

According to Scheme 4 Step 4b of the general methodology, methyl 6-(3-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-ylamino) nicotinate (0.17 mmol, 60 mg) was suspended in 32% NH_4OH solution and the mixture was heated in a closed vessel at 100°C under microwaves irradiation for 1h. After cooling, a precipitate was formed. The solid was recovered by filtration and washed with little MeOH affording 6-(3-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-ylamino)-nicotinamide (0.047 mmol, 16 mg, 28%) as a white solid.

LC (Method LC-E): RT = 1.42 min; MS *m/z* ES+= 342.

^{1}H NMR (300 MHz, DMSO-d6) δ ppm: 12.49 (br. s., 1 H), 8.92 (d, 1 H), 8.25 (s, 1 H), 8.23 (dd, 1 H), 7.99 (br. s., 1 H), 7.90 (s, 1 H), 7.41 (br. s., 1 H), 7.17 (d, 1 H), 4.04 (d, 2 H), 1.14 - 1.43 (m, 1 H), 0.51 - 0.62 (m, 2 H), 0.33 - 0.44 (m, 2 H).

EXAMPLE 11: N-(Pyridin-2-yl)-4-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)thiazol-2-amine (Final compound 1-87)

11.1 : 1-(2,2,2-Trifluoroethyl)-1H-pyrazole-4-carboxylic acid (h1)

According to Scheme 2 Step 1 of the general methodology, ethyl 1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carboxylate (1.03 mmol, 230 mg) was suspended in a mixture of HCl 37% aqueous solution (2 mL) and dioxane (3 mL) and the mixture was heated overnight at reflux. The reaction mixture was concentrated to dryness affording 1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carboxylic acid (1.03 mmol, 200 mg, 100%) as an off white solid. The crude product was used without further purification.

LC (Method LC-D): RT = 0.79 min; MS *m/z* ES^-= 195.

11.2: 1-(2,2,2-Trifluoroethyl)-1H-pyrazole-4-carbonyl chloride (i1)

According to Scheme 2 Step 2 of the general methodology: A solution of 1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carboxylic acid (1.03 mmol, 200 mg), oxalyl chloride (2.58 mmol, 0.22 mL) and two drops of DMF in DCM (5 mL) was stirred for 4 hours at room temperature. After evaporation of the solvent, 1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carbonyl chloride (1.03 mmol, 219 mg) was obtained as a brown oil. The crude product was used without further purification.

LC (Method LC-B): RT = 1.11 min; MS *m/z* ES^-= 209 (methyl ester).

The following compounds are synthesized according to the same method starting from commercially available acid (h2) or from the freshly prepared acid described below :

Cpd	IUPAC Name	Method LC-MS; RT (min)	(MH^+)
i2	3-Methyl-1-propyl-1H-pyrazole-4-carbonyl chloride	LC-D; 1.08,	183 (methyl ester)
i3	1-Propyl-1H-pyrazole-4-carbonyl chloride	LC-D; 0.98	169 (methyl ester)
i4	1-(Cyclopropylmethyl)-1H-pyrazole-4-carbonyl chloride	LC-D; 0.97	181 (methyl ester)

Cpd	IUPAC Name	Method LC-MS; RT (min)	(MH^+)
i5	1-Propyl-3-(trifluoromethyl)-1H-pyrazole-4-carbonyl chloride	LC-B; 1.43	237 (methyl ester)

The carboxylic acids h3, h4, and h5, used for the synthesis of intermediate compounds i3, i4 and i5, are prepared according to the following procedure:

1-Propyl-1H-pyrazole-4-carboxylic acid (h3)

According to Scheme 2 Step 1 of the general methodology, ethyl 1-Propyl-1H-pyrazole-4-carboxylate (4.39 mmol, 801 mg) was dissolved in a 1:1 mixture of THF and MeOH (15 mL). A solution of LiOH (2N, 10.54 mmol, 5.27 mL) was added and the mixture was heated at reflux for 96 hours. The reaction mixture was concentrated and partioned between NaOH 1N and AcOEt. The aqueous layer was separated, acidified with HCl 12N (pH=1) and extracted with DCM. The organic layer was separated, dried over Na_2SO_4 and concentrated to dryness affording 1-propyl-1H-pyrazole-4-carboxylic acid (3.85 mmol, 594 mg, 88 %) as an off white solid. The crude product was used without further purification.

LC (Method LC-D): RT = 0.71 min; MS *m/z* ES^- = 155.

The following compounds are synthesized according to the same method using NaOH instead of LiOH:

Cpd	IUPAC Name	Method LC-MS; RT (min)	(MH^+)
h4	1-(Cyclopropylmethyl)-1H-pyrazole-4-carboxylic acid	LC-B; 0.85	167
h5	1-Propyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid	LC-D; 1.12	223

11.3: 2-Bromo-1-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)ethanone (j1) and 2-chloro-1-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)ethanone (k1)

According to Scheme 2 Step 3 of the general methodology, a solution of TMSdiazomethane (3.90 mmol, 1.95 mL) was added to a solution of 1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carbonyl chloride i1 (1.03 mmol, 219 mg) in acetonitrile (5 mL) at 0°C. The reaction mixture was stirred at room temperature overnight. After cooling to 0°C, HBr (4.16 mmol, 0.7 mL, 48%) was added to the reaction mixture. The reaction mixture was stirred at room temperature for two hour. AcOEt and water were added to the reaction mixture and the organic layer was separated. The aqueous phase was neutralized with 1M NaOH solution and extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 2-bromo-1-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)ethanone and 2-chloro-1-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)ethanone in a ratio (54/34 by LC-MS peaks integration at 254nm) (105 mg) as a brown gummy solid. The crude product was used without further purification.

LC (Method LC-B): RT = 1.18; 1.13 min; MS *m/z* ES^-= 271.1; 227.

The following compounds are synthesized according to the same method:

Cpds	IUPAC Name (ratio by LC-MS peaks integration at 254 nm)	Method LC-MS; RT (min)	(MH^+)
j2/k2	2-Bromo-1-(3-methyl-1-propyl-1H-pyrazol-4-yl)ethanone / 2-chloro-1-(3-methyl-1-propyl-1H-pyrazol-4-yl)ethanone (60/39)	LC-D; 1.09/1.04	245/ 201
j3/k3	2-Bromo-1-(1-propyl-1H-pyrazol-4-yl)ethanone / 2-chloro-1-(1-propyl-1H-pyrazol-4-yl)ethanone (89/11)	LC-D; 1.06 /1.01	231/187
j4/k4	2-Bromo-1-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)ethanone / 2-chloro-1-	LC-D; 1.08 / 1.03	243/ 199

Cpds	IUPAC Name (ratio by LC-MS peaks integration at 254 nm)	Method LC-MS; RT (min)	(MH^+)
	(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)ethanone (84 /11)		
j5/k5	2-Bromo-1-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)ethanone / 2-chloro-1-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)ethanone (86/14)	LC-B; 1.45/1.42	299/ 255

11.4 1-(2-Methoxypyridin-3-yl)thiourea (m1)

3-Isothiocyanato-2-methoxypyridine (1.20 mmol, 200 mg) was dissolved in 2M methanolic ammonia and the reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated to dryness affording 1-(2-methoxypyridin-3-yl)thiourea (218 mg) as and off white solid.

LC (Method LC-D): RT = 0.57 min; MS *m/z* ES^-= 184.

The following compounds are synthesized according to the same method

Cpd	IUPAC Name	Method LC-MS; RT (min)	(MH^+)	From d
m2	1-(6-methoxypyridin-3-yl)thiourea	LC-D; 0.55	184	d3

11.5: N-(pyridin-2-yl)-4-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)thiazol-2-amine (Final compound 1-87)

According to Scheme 2 Step 4 of the general methodology, a solution of 2-bromo-1-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)ethanone and 2-chloro-1-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)ethanone (0.38 mmol, 105 mg) and of 1-(pyridin-2-

yl)thiourea (CAS 14294-11-2, 0.26 mmol, 40 mg) in absolute ethanol (5 mL) was stirred under reflux for 20 minutes. After evaporation of the solvent, AcOEt was added and the organic phase was washed with a 1M NaOH solution and brine. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel using DCM/MeOH/32% NH_4OH (99:1:0.1) as eluent to yield N-(pyridin-2-yl)-4-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)thiazol-2-amine (0.06 mmol, 20 mg, 16%) as a white solid.

LC (Method LC-E): RT = 1.50 min; MS *m/z* ES^+= 326.

^1H NMR (300 MHz, DMSO-d_6) δ ppm: 11.33 (br. s., 1 H) 8.25 - 8.32 (m, 1 H) 8.09 (s, 1 H) 7.93 (d, 1 H) 7.64 - 7.74 (m, 1 H) 7.04 - 7.11 (m, 2 H) 6.89 - 6.95 (m, 1 H) 5.17 (q, 2 H).

The following compounds are synthesized according to the same method:

Cpd	IUPAC Name	Method LC-MS; RT (min)	(MH^+)	From j/k	From m or [CAS]
1-77	4-(1-Propyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)thiazol-2-amine	LC-E; 1.48	286	j3/k3	[14294-11-2]
1-78	N-(Benzo[d][1,3]dioxol-5-yl)-4-(1-propyl-1H-pyrazol-4-yl)thiazol-2-amine	LC-E; 1.81	329	j3/k3	[65069-55-8]
1-79	N-(2-Fluorophenyl)-4-(1-propyl-1H-pyrazol-4-yl)thiazol-2-amine	LC-E; 2.15	303	j3/k3	[656-32-6]

Cpd	IUPAC Name	Method LC-MS; RT (min)	(MH^+)	From j/k	From m or [CAS]
1-80	4-(3-Methyl-1-propyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)thiazol-2-amine	LC-E; 1.51	300	j2/k2	[14294-11-2]
1-81	4-(3-Methyl-1-propyl-1H-pyrazol-4-yl)-N-(6-methylpyridin-2-yl)thiazol-2-amine	LC-E; 1.60	314	j2/k2	[49600-34-2]
1-82	N-(5-Chloropyridin-2-yl)-4-(3-methyl-1-propyl-1H-pyrazol-4-yl)thiazol-2-amine	LC-E; 2.29	334	j2/k2	[31430-27-0]
1-83	N-(6-Methoxypyridin-3-yl)-4-(3-methyl-1-propyl-1H-pyrazol-4-yl)thiazol-2-amine	LC-E; 1.73	330	j2/k2	m2
1-84	N-(2-Methoxypyridin-3-yl)-4-(3-methyl-1-propyl-1H-pyrazol-4-yl)thiazol-2-amine	LC-E; 2.05	330	j2/k2	m1
1-85	4-(1-Propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)thiazol-2-amine	LC-E; 1.87	354	j5/k5	[14294-11-2]
1-86	4-(1-	LC-E; 1.45	298	j4/k4	[14294-11-2]

Cpd	IUPAC Name	Method LC-MS; RT (min)	(MH^+)	From j/k	From m or [CAS]
	(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)thiazol-2-amine				

Table 3 : Physico-chemical data for some compounds (nd = not determined).

Cpd	Melting point (°C)	MW (theor)	[MH^+]	LC-MS Method	RT (min)	Physical form
1-1	nd	395.45	396	LC-A	2.80	White solid
1-2	nd	395.45	396	LC-A	2.80	White solid
1-3	nd	378.45	379	LC-A	2.50	White solid
1-4	nd	378.45	379	LC-A	2.57	White solid
1-5	180-184	363.44	364	LC-A	2.60	White solid
1-6	206-208	376.47	377	LC-A	2.74	White solid
1-7	206-208	376.47	377	LC-A	2.74	White solid
1-8	193-197	333.41	334	LC-A	2.85	White solid
1-9	156-158	300.38	301	LC-A	2.26	White solid
1-10	220-225	332.42	333	LC-A	2.73	Yellow solid
1-11	160	285.37	286	LC-A	1.91	White solid
1-12	176	271.34	272	LC-A	1.82	White solid
1-13	254-256	257.31	258	LC-A	1.63	Beige solid
1-14	196-197	272.32	273	LC-E	1.65	Brown powder

Cpd	Melting point (°C)	MW (theor)	[MH+]	LC-MS Method	RT (min)	Physical form
1-15	243-244	302.35	303	LC-E	1.82	Yellow powder
1-16	278-280	357.42	358	LC-E	1.74	Yellow powder
1-17	203-205	286.35	287	LC-E	1.70	Light brown powder
1-18	233-234	286.35	287	LC-E	1.76	Pale brown powder
1-19	nd	352.39	353	LC-E	2.15	Off-white powder
1-20	189-190	351.39	352	LC-E	2.40	Off-white powder
1-21	245-247	342.42	343	LC-E	1.73	Brown powder
1-22	236-237	298.36	299	LC-E	1.88	Off-white powder
1-22a	222-224	298.36	299	LC-E	1.80	pale yellow powder.
1-23	253-255	312.39	313	LC-F	3.06	Grey powder
1-24	nd	326.42	327	LC-E	2.20	White powder
1-25	nd	316.35	317	LC-E	2.04	Light brown powder
1-26	nd	316.35	317	LC-E	1.94	Dark yellow solid
1-27	nd	328.39	329	LC-E	2.04	Brown powder
1-28	194-196	368.45	369	LC-E	2.37	Brown powder
1-29	nd	383.47	384	LC-E	1.94	Light brown powder
1-30	289-290	383.47	384	LC-E	1.71	Dark yellow powder
1-31	nd	366.35	367	LC-E	2.21	Off-white solid
1-32	nd	332.80	333	LC-E	2.15	Off white solid
1-33	nd	323.38	324	LC-E	1.89	Pale yellow solid
1-34	268-269	299.35	300	LC-E	1,64	White solid
1-35	nd	341.39	342	LC-E	1.42	White solid
1-36	243-245	312.39	313	LC-E	2.06	Light brown powder
1-37	258-259	357.42	358	LC-E	1.36	Light brown powder
1-38	223-224	328.39	329	LC-E	1.66	Light brown powder

Cpd	Melting point (°C)	MW (theor)	[MH+]	LC-MS Method	RT (min)	Physical form
1-39	300-301	326.29	327	LC-E	1.96	Light brown powder
1-40	197-198	302.35	303	LC-E	1.54	Light brown powder
1-41	nd	288.32	289	LC-E	1.40	Beige solid
1-42	216-218	298.36	299	LC-E	1.86	Light brown powder
1-43	nd	368.39	369	LC-E	2.17	Pale pink solid
1-44	281-282	352.39	353	LC-E	2.37	Brown powder
1-45	202-204	351.39	352	LC-E	2.53	White powder
1-46	nd	354.35	355	LC-E	2.44	White powder
1-47	nd	368.38	369	LC-E	2.61	White powder
1-48	nd	384.38	385	LC-E	2.34	White powder
1-49	nd	384.38	385	LC-E	2.60	White powder
1-50	nd	388.79	389	LC-E	2.77	Light brown powder
1-51	nd	422.35	423	LC-E	2.81	Pale yellow powder
1-52	nd	390.32	391	LC-F	3.83	Off white powder
1-53	nd	404.41	405	LC-E	2.82	Pale yellow powder
1-54	nd	368.38	369	LC-E	1.69	Yellow gummy solid
1-55	nd	371.35	372	LC-E	2.71	Pale yellow oil
1-56	nd	389.35	390	LC-E	2.75	White powder
1-57	nd	397.36	398	LC-E	2.55	Pale yellow powder
1-58	nd	438.47	439	LC-E	2.06	Pale yellow powder
1-59	nd	383.39	384	LC-E	2.67	Yellow gummy solid
1-60	nd	421.35	422	LC-E	2.91	Yellow powder
1-61	nd	387.80	388	LC-E	2.91	White powder
1-62	155-156	366.35	367	LC-E	3.18	Off-white powder
1-63	nd	394.29	395	LC-E	2.50	White solid

Cpd	Melting point (°C)	MW (theor)	[MH+]	LC-MS Method	RT (min)	Physical form
1-64	227-228	314.41	315	LC-E	2.06	Light brown powder
1-65	225-226	326.42	327	LC-E	2.03	Light brown powder
1-66	186-188	340.45	341	LC-E	2.16	White powder
1-67	nd	314.41	315	LC-E	2.17	White solid
1-68	nd	328.44	329	LC-E	2.26	White powder
1-69	nd	368.38	369	LC-E	2.33	White solid
1-70	nd	368.38	369	LC-E	2.27	Light orange solid
1-71	nd	334.82	335	LC-E	2.24	Pale yellow solid
1-72	nd	318.36	319	LC-E	2.07	Light brown solid
1-73	nd	325.39	326	LC-E	1.94	Brown solid
1-74	nd	385.48	386	LC-E	2.02	Yellow powder
1-75	nd	330.41	331	LC-E	2.14	Yellow powder
1-76	nd	318.36	319	LC-E	2.12	Pale yellow powder
1-77	nd	285.36	286	LC-E	1,48	Pale yellow solid
1-78	nd	328.39	329	LC-E	1.81	Dark red solid
1-79	nd	302.36	303	LC-E	2.15	Yellow gummy solid
1-80	nd	299.39	300	LC-E	1.51	Yellow foam
1-81	nd	313.42	314	LC-E	1.60	Orange foam
1-82	nd	333.83	334	LC-E	2,29	White foam
1-83	nd	329.42	330	LC-E	1.73	Pale orange foam
1-84	nd	329.42	330	LC-E	2.05	Pale orange foam
1-85	108-110	353.36	354	LC-E	1.87	Pale yellow powder
1-86	194-196	297.38	298	LC-E	1.45	Light brown powder
1-87	nd	325.30	326	LC-E	1.50	Yellow powder
1-88	191	300.38	301	LC-A	1.51	White solid

Cpd	Melting point (°C)	MW (theor)	[MH+]	LC-MS Method	RT (min)	Physical form
2-1	nd	285.37	286	LC-A	4.21	Colorless oil
2-2	nd	285.37	286	LC-A	4.31	Colorless oil

Table 4 : ^{1}H-NMR spectra for some compounds:

Cpd	IUPAC Name	^{1}H-NMR (300 MHz, solvent), δ ppm
1-5	3-(1-(4-methoxybenzyl)-1H-pyrazol-4-yl)-N-phenyl-1,2,4-thiadiazol-5-amine	(DMSO-d6): δ ppm: 10.98 (1H, s), 8.37 (1H, s), 7.93 (1H, s), 7.59 (2H, d), 7.40 (2H, t), 7.27 (2H, d), 7.08 (1H,t), 6.92 (2H, d), 5.32 (2H,s), 3.73 (3H, s).
1-8	3-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-N-phenyl-1,2,4-thiadiazol-5-amine	(DMSO-d6): δ ppm: 11.03 (1H, s), 8.15 (1H, s), 7.59 (6H, m), 7.50 (1H, m), 7.42 (2H, t), 7.09 (1H, t), 2.70 (3H, s).
1-9	3-(3-methyl-1-propyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine	($CDCl_3$) δ ppm: 8.45 (1H, m), 7.94 (1H, s), 7.60 (H, m), 6.99 (1H, m), 6.76 (1H, d), 3.99 (2H, t), 2.64 (3H, s), 1.84 (2H, m), 0.89 (3H, t).
1-10	4-(1-benzyl-1H-pyrazol-4-yl)-N-phenylthiazol-2-amine	($CDCl_3$) δ ppm: 10.23 (1H, bs), 8.17 (1H, s), 7.86 (1H, s), 7.67 (2H, d), 7.30 (7H, m), 6.95 (1H, t), 6.90 (1H, s), 5.37 (2H, s).
1-11	4-(1-isopropyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)thiazol-2-amine	(DMSO-d6) δ ppm: 11.3 (s, 1H), 8.3 (d, 1H), 8.0 (s, 1H), 7.8 (s, 1H), 7.6-7.7 (m, 1H), 7.1 (d, 1H), 7.0 (s, 1H), 6.8-6.9 (m, 1H), 4.4-4.6 (m, 1H), 1.4 (d, 6H)
1-12	4-(1-ethyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)thiazol-2-amine	(DMSO-d6) δ ppm:, 8.0 (s, 1H), 7.8 (s, 1H), 7.6-7.7 (m, 1H), 7.1 (d, 1H), 7.0 (s, 1H), 6.8-6.9 (m, 1H), 2.03 (q, 2H), 1.4 (t, 3H)
1-13	4-(1-methyl-1H-pyrazol-4-yl)-	(DMSO-d6) δ ppm: 11.3 (s, 1H), 8.3 (d, 1H),

Cpd	IUPAC Name	^{1}H-NMR (300 MHz, solvent), δ ppm
	N-(pyridin-2-yl)thiazol-2-amine	8.0 (s, 1H), 7.8 (s, 1H), 7.6-7.7 (m, 1H), 7.1 (d, 1H), 7.0 (s, 1H), 6.8-6.9 (m, 1H), 3.9 (s, 3H)
1-14	3-(1-Ethyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 12.19 (s, 1 H), 8.42 (ddd, 1 H), 8.22 (d, 1 H), 7.89 (d, 1 H), 7.82 (ddd, 1 H), 7.15 (dt, 1 H), 7.06 (ddd, 1 H), 4.20 (q, 2 H), 1.41 (t, 3 H)
1-15	3-(1-Ethyl-1H-pyrazol-4-yl)-N-(6-methoxypyridin-2-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 12.12 (s, 1 H) 8.21 (d, 1 H) 7.88 (d, 1 H) 7.71 (t, 1 H) 6.70 (d, 1 H) 6.45 (d, 1 H) 4.21 (q, 2 H) 4.07 (s, 3 H) 1.41 (t, 3 H)
1-16	3-(1-Ethyl-1H-pyrazol-4-yl)-N-(6-morpholinopyridin-2-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 11.90 (s, 1 H), 8.18 (d, 1 H), 7.87 (d, 1 H), 7.56 (dd, 1 H), 6.35 - 6.53 (m, 2 H), 4.20 (q, 2 H), 3.70 - 3.85 (m, 4 H), 3.49 - 3.63 (m, 4 H), 1.41 (t, 3 H)
1-17	3-(1-Ethyl-3-methyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine	($CDCl_3$) δ ppm: 9.93 (s, 1 H) 8.46 (ddd, 1 H) 7.92 (s, 1 H) 7.60 (ddd, 1 H) 6.93 - 7.03 (m, 1 H) 6.71 (dt, 1 H) 4.11 (q, 2 H) 2.66 (s, 3 H) 1.45 (t, 3 H)
1-18	3-(1-Propyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 12.19 (br. s., 1 H) 8.39 - 8.46 (m, 1 H) 8.21 (s, 1 H) 7.89 (s, 1 H) 7.77 - 7.86 (m, 1 H) 7.12 - 7.19 (m, 1 H) 7.02 - 7.09 (m, 1 H) 4.13 (t, 2 H) 1.75 - 1.90 (m, 2 H) 0.85 (t, 3 H)
1-19	3-(1-(3-Fluorobenzyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 12.20 (br. s., 1 H) 8.42 (ddd, 1 H) 8.36 (d, 1 H) 7.94 (d, 1 H) 7.75 - 7.88 (m, 1 H) 7.33 - 7.48 (m, 1 H) 6.95 - 7.22 (m, 5 H) 5.44 (s, 2 H)
1-20	3-(1-(3-Fluorobenzyl)-1H-pyrazol-4-yl)-N-phenyl-1,2,4-	(DMSO-d6) δ ppm: 10.95 (s, 1 H) 8.45 (s, 1 H) 7.98 (s, 1 H) 7.55 - 7.65 (m, 2 H) 7.35 - 7.46 (m,

Cpd	IUPAC Name	^{1}H-NMR (300 MHz, solvent), δ ppm
	thiadiazol-5-amine	3 H) 7.01 - 7.20 (m, 4 H) 5.44 (s, 2 H)
1-21	N-(Pyridin-2-yl)-3-(1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 12.20 (br. s., 1 H) 8.42 (ddd, 1 H) 8.20 (s, 1 H) 7.90 (s, 1 H) 7.73 - 7.86 (m, 1 H) 7.11 - 7.21 (m, 1 H) 6.98 - 7.10 (m, 1 H) 4.08 (d, 2 H) 3.73 - 3.91 (m, 2 H) 3.19 - 3.26 (m, 2 H) 2.00 - 2.19 (m, 1 H) 1.34 - 1.48 (m, 2 H) 1.18 - 1.34 (m, 2 H)
1-22	3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(pyridine-2-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 12.20 (br. s., 1 H) 8.39 - 8.45 (m, 1 H) 8.24 (s, 1 H) 7.89 (d, 1 H) 7.77 - 7.86 (m, 1 H) 7.11 - 7.19 (m, 1 H) 7.01 - 7.09 (m, 1 H) 4.04 (d, 2 H) 1.21 - 1.38 (m, 1 H) 0.51 - 0.62 (m, 2 H) 0.35 - 0.44 (m, 2 H)
1-22a	3-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine hydrochloride	(DMSO-d_6) δ ppm 12.22 (s, 1 H), 8.39 - 8.45 (m, 1 H), 8.25 (d, 1 H), 7.89 (d, 1 H), 7.77 - 7.86 (m, 1 H), 7.12 - 7.19 (m, 1 H), 7.02 - 7.10 (m, 1 H), 4.04 (d, 2 H), 1.19 - 1.39 (m, 1 H), 0.51 - 0.60 (m, 2 H), 0.35 - 0.44 (m, 2 H)
1-23	3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(6-methylpyridin-2-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 12.14 (br. s., 1 H) 8.24 (d, 1 H) 7.89 (d, 1 H) 7.71 (dd, 1 H) 6.86 - 7.00 (m, 2 H) 4.04 (d, 2 H) 2.53 (s, 3 H) 1.20 - 1.37 (m, 1 H) 0.50 - 0.63 (m, 2 H) 0.32 - 0.44 (m, 2 H)
1-24	3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(6-ethylpyridin-2-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 12.14 (br. s., 1 H) 8.24 (s, 1 H) 7.89 (s, 1 H) 7.67 - 7.77 (m, 1 H) 6.86 - 7.01 (m, 2 H) 4.04 (d, 2 H) 2.82 (q, 2 H) 1.34 (t, 3 H) 1.21 - 1.32 (m, 1 H) 0.51 - 0.62 (m, 2 H) 0.34 - 0.45 (m, 2 H)
1-25	3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(6-	(DMSO-d6) δ ppm: 12.47 (br. s., 1 H) 8.26 (s, 1 H) 7.91 - 8.02 (m, 1 H) 7.90 (s, 1 H) 7.03 (dd, 1

Cpd	IUPAC Name	^{1}H-NMR (300 MHz, solvent), δ ppm
	fluoropyridin-2-yl)-1,2,4-thiadiazol-5-amine	H) 6.71 - 6.80 (m, 1 H) 4.04 (d, 2 H) 1.19 - 1.38 (m, 1 H) 0.51 - 0.60 (m, 2 H) 0.36 - 0.44 (m, 2 H)
1-26	3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(5-fluoropyridin-2-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 12.28 (br. s., 1 H) 8.44 (d, 1 H) 8.25 (s, 1 H) 7.89 (s, 1 H) 7.74 - 7.87 (m, 1 H) 7.19 (dd, 1 H) 4.04 (d, 2 H) 1.19 - 1.38 (m, 1 H) 0.49 - 0.62 (m, 2 H) 0.33 - 0.44 (m, 2 H)
1-27	3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(6-methoxypyridin-2-yl)-1,2,4-thiadiazol-5-amine	($CDCl_3$) δ ppm: 8.17 (s, 1 H) 8.09 (s, 1 H) 7.60 (t, 1 H) 6.42 - 6.56 (m, 2 H) 4.18 (s, 3 H) 4.05 (d, 2 H) 1.29 - 1.43 (m, 1 H) 0.66 - 0.76 (m, 2 H) 0.38 - 0.47 (m, 2 H)
1-28	N-(6-Cyclobutoxypyridin-2-yl)-3-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 12.12 (s, 1 H) 8.24 (s, 1 H) 7.89 (s, 1 H) 7.70 (t, 1 H) 6.70 (d, 1 H) 6.41 (d, 1 H) 5.34 - 5.50 (m, 1 H) 4.04 (d, 2 H) 2.56 (br. s., 2 H) 2.00 - 2.22 (m, 2 H) 1.62 - 1.93 (m, 2 H) 1.17 - 1.35 (m, 1 H) 0.47 - 0.64 (m, 2 H) 0.34 - 0.47 (m, 2 H)
1-29	3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(6-morpholinopyridin-2-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 11.91 (br. s., 1 H) 8.21 (s, 1 H) 7.87 (s, 1 H) 7.51 - 7.61 (m, 1 H) 6.39 - 6.49 (m, 2 H) 4.04 (d, 2 H) 3.72 - 3.84 (m, 4 H) 3.52 - 3.63 (m, 4 H) 1.25 - 1.36 (m, 1 H) 0.51 - 0.60 (m, 2 H) 0.35 - 0.44 (m, 2 H)
1-30	3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(5-morpholinopyridin-2-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 11.95 (s, 1 H) 8.22 (s, 1 H) 8.07 (d, 1 H) 7.88 (s, 1 H) 7.57 (dd, 1 H) 7.06 (d, 1 H) 4.03 (d, 2 H) 3.69 - 3.81 (m, 4 H) 3.02 - 3.16 (m, 4 H) 1.20 - 1.36 (m, 1 H) 0.49 - 0.62 (m, 2 H) 0.33 - 0.45 (m, 2 H)
1-31	3-(1-(Cyclopropylmethyl)-1H-	(DMSO-d6) δ ppm: 12.63 (br. s., 1 H) 8.27 (s, 1

Cpd	IUPAC Name	^{1}H-NMR (300 MHz, solvent), δ ppm
	pyrazol-4-yl)-N-(6-(trifluoromethyl)pyridin-2-yl)-1,2,4-thiadiazol-5-amine	H) 8.06 (dd, 1 H) 7.91 (s, 1 H) 7.53 (d, 1 H) 7.40 (d, 1 H) 4.04 (d, 2 H) 1.19 - 1.40 (m, 1 H) 0.51 - 0.61 (m, 2 H) 0.35 - 0.44 (m, 2 H)
1-32	N-(5-Chloropyridin-2-yl)-3-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	($CDCl_3$) δ ppm: 8.44 (dd, 1 H) 8.16 (s, 1 H) 8.09 (s, 1 H) 7.66 (dd, 1 H) 6.88 (d, 1 H) 4.05 (d, 2 H) 1.22 - 1.41 (m, 1 H) 0.65 - 0.74 (m, 2 H) 0.36 - 0.46 (m, 2 H)
1-33	6-(3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-ylamino)nicotinonitrile	(DMSO-d6) δ ppm: 12.77 (br. s., 1 H) 8.91 (dd, 1 H) 8.27 (s, 1 H) 8.20 (dd, 1 H) 7.91 (s, 1 H) 7.23 (d, 1 H) 4.04 (d, 2 H) 1.19 - 1.37 (m, 1 H) 0.50 - 0.60 (m, 2 H) 0.35 - 0.44 (m, 2 H)
1-34	3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(pyrazin-2-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 12.65 (br. s., 1 H), 8.55 (d, 1 H), 8.46 (dd, 1 H), 8.23 - 8.31 (m, 2 H), 7.92 (d, 1 H), 4.05 (d, 2 H), 1.18 - 1.42 (m, 1 H), 0.52 - 0.61 (m, 2 H), 0.34 - 0.44 (m, 2 H)
1-35	6-(3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-ylamino)nicotinamide	(DMSO-d6) δ ppm: 12.49 (br. s., 1 H), 8.92 (d, 1 H), 8.25 (s, 1 H), 8.23 (dd, 1 H), 7.99 (br. s., 1 H), 7.90 (s, 1 H), 7.41 (br. s., 1 H), 7.17 (d, 1 H), 4.04 (d, 2 H), 1.14 - 1.43 (m, 1 H), 0.51 - 0.62 (m, 2 H), 0.33 - 0.44 (m, 2 H)
1-36	3-(1-(Cyclobutylmethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 12.19 (s, 1 H) 8.37 - 8.47 (m, 1 H) 8.18 (s, 1 H) 7.88 (s, 1 H) 7.77 - 7.86 (m, 1 H) 7.15 (d, 1 H) 7.01 - 7.09 (m, 1 H) 4.20 (d, 2 H) 2.73 - 2.87 (m, 1 H) 1.72 - 2.05 (m, 6 H)
1-37	3-(1-(2-Morpholinoethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 12.19 (br. s., 1 H) 8.42 (ddd, 1 H) 8.23 (s, 1 H) 7.89 (s, 1 H) 7.76 - 7.86 (m, 1 H) 7.12 - 7.20 (m, 1 H) 7.01 - 7.10 (m, 1

Cpd	IUPAC Name	^{1}H-NMR (300 MHz, solvent), δ ppm
		H) 4.30 (t, 2 H) 3.49 - 3.60 (m, 4 H) 2.75 (t, 2 H) 2.36 - 2.46 (m, 4 H)
1-38	N-(Pyridin-2-yl)-3-(1-((tetrahydrofuran-2-yl)methyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 12.20 (br. s., 1 H) 8.36 - 8.48 (m, 1 H) 8.18 (s, 1 H) 7.89 (s, 1 H) 7.76 - 7.87 (m, 1 H) 7.15 (d, 1 H) 6.97 - 7.11 (m, 1 H) 4.11 - 4.32 (m, 3 H) 3.54 - 3.83 (m, 2 H) 1.70 - 2.02 (m, 3 H) 1.47 - 1.70 (m, 1 H)
1-39	N-(Pyridin-2-yl)-3-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 12.24 (br. s., 1 H) 8.40 - 8.47 (m, 1 H) 8.35 (s, 1 H) 8.03 (s, 1 H) 7.78 - 7.88 (m, 1 H) 7.16 (dt, 1 H) 7.07 (ddd, 1 H) 5.23 (q, 2 H)
1-40	3-(1-(2-Methoxyethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 12.20 (s, 1 H) 8.42 (ddd, 1 H) 8.19 (s, 1 H) 7.90 (s, 1 H) 7.76 - 7.86 (m, 1 H) 7.12 - 7.18 (m, 1 H) 7.02 - 7.09 (m, 1 H) 4.34 (t, 2 H) 3.72 (t, 2 H) 3.25 (s, 3 H)
1-41	2-(4-(5-(Pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)-1H-pyrazol-1-yl)ethanol	(DMSO-d6) δ ppm: 12.19 (s, 1 H), 8.35 - 8.48 (m, 1 H), 8.19 (s, 1 H), 7.89 (s, 1 H), 7.76 - 7.86 (m, 1 H), 7.10 - 7.20 (m, 1 H), 6.98 - 7.10 (m, 1 H), 4.21 (t, 2 H), 3.71 - 3.82 (m, 3 H)
1-42	3-(1-Cyclobutyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 12.20 (s, 1 H) 8.38 - 8.46 (m, 1 H) 8.26 (s, 1 H) 7.93 (s, 1 H) 7.77 - 7.87 (m, 1 H) 7.12 - 7.19 (m, 1 H) 7.01 - 7.10 (m, 1 H) 4.85 - 5.00 (m, 1 H) 2.52 - 2.65 (m, 2 H) 2.34 - 2.47 (m, 2 H) 1.75 - 1.90 (m, 2 H)
1-43	3-(1-(3-Fluoro-4-methoxyphenyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 12.15 (br. s., 1 H) 8.91 (s, 1 H) 8.44 (ddd, 1 H) 8.17 (s, 1 H) 7.80 - 7.93 (m, 2 H) 7.68 - 7.78 (m, 1 H) 7.32 (dd, 1 H) 7.15 - 7.23 (m, 1 H) 7.00 - 7.12 (m, 1 H) 3.90 (s, 3 H)

Cpd	IUPAC Name	^{1}H-NMR (300 MHz, solvent), δ ppm
1-44	3-(1-(4-Fluorophenyl)-5-methyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 12.22 (s, 1 H) 8.39 - 8.48 (m, 1 H) 8.09 (s, 1 H) 7.78 - 7.89 (m, 1 H) 7.64 (m, 2 H) 7.41 (m, 2 H) 7.18 (d, 1 H) 7.01 - 7.12 (m, 1 H) 2.70 (s, 3 H)
1-45	3-(1-(4-Fluorophenyl)-5-methyl-1H-pyrazol-4-yl)-N-phenyl-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 10.97 (br. s., 1 H) 8.13 (s, 1 H) 7.55 - 7.72 (m, 4 H) 7.31 - 7.49 (m, 4 H) 7.09 (dd, 1 H) 2.68 (s, 3 H)
1-46	3-(1-Propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine	($CDCl_3$) δ ppm: 8.95 (br. s., 1 H) 8.38 - 8.59 (m, 1 H) 8.11 (s, 1 H) 7.66 - 7.90 (m, 1 H) 6.91 - 7.09 (m, 2 H) 4.10 - 4.25 (m, 2 H) 1.90 - 2.08 (m, 2 H) 0.98 (t, 3 H)
1-47	N-(6-Methylpyridin-2-yl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	($CDCl_3$) δ ppm: 9.06 (br. s., 1 H) 8.11 (s, 1 H) 7.54 - 7.71 (m, 1 H) 6.89 (d, 1 H) 6.71 - 6.87 (m, 1 H) 4.17 (t, 2 H) 2.63 (s, 3 H) 1.89 - 2.06 (m, 2 H) 0.99 (t, 3 H)
1-48	N-(6-Methoxypyridin-3-yl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 10.83 (s, 1 H) 8.57 (s, 1 H) 8.52 (d, 1 H) 8.02 (dd, 1 H) 6.86 (d, 1 H) 4.21 (t, 2 H) 3.85 (s, 3 H) 1.72 - 1.95 (m, 2 H) 0.85 (t, 3 H)
1-49	N-(2-Methoxypyridin-3-yl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 8.85 (d, 1 H) 8.60 (s, 1 H) 8.55 (s, 1 H) 7.85 (dd, 1 H) 7.04 (dd, 1 H) 4.22 (t, 2 H) 4.00 (s, 3 H) 1.78 - 1.94 (m, 2 H) 0.86 (t, 3 H)
1-50	N-(5-Chloropyridin-2-yl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 12.30 (br. s., 1 H) 8.51 (d, 1 H) 8.45 (s, 1 H) 7.95 (dd, 1 H) 7.25 (d, 1 H) 4.22 (t, 2 H) 1.77 - 1.92 (m, 2 H) 0.86 (t, 3 H)
1-51	3-(1-Propyl-3-(trifluoromethyl)-	(DMSO-d6) δ ppm: 12.48 (br. s., 1 H) 8.71 (d, 1

Cpd	IUPAC Name	^{1}H-NMR (300 MHz, solvent), δ ppm
	1H-pyrazol-4-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)-1,2,4-thiadiazol-5-amine	H) 8.44 - 8.50 (m, 1 H) 7.47 - 7.52 (m, 1 H) 7.37 - 7.44 (m, 1 H) 4.18 - 4.27 (m, 2 H) 1.79 - 1.93 (m, 2 H) 0.87 (t, 3 H)
1-52	N-(3,5-Difluoropyridin-2-yl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 8.35 - 8.46 (m, 2 H) 7.97 - 8.15 (m, 1 H) 4.23 (t, 2 H) 1.76 - 1.95 (m, 2 H) 0.86 (t, 3 H)
1-53	3-(1-Propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-N-(quinolin-2-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 12.51 (br. s., 1 H) 8.47 (d, 1 H) 8.36 (d, 1 H) 8.00 (d, 1 H) 7.89 - 7.96 (m, 1 H) 7.71 - 7.82 (m, 1 H) 7.45 - 7.55 (m, 1 H) 7.39 (d, 1 H) 4.24 (t, 2 H) 1.78 - 1.95 (m, 2 H) 0.88 (t, 3 H)
1-54	N-(2-Methylpyridin-4-yl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 11.10 (br. s., 1 H) 8.62 (s, 1 H) 8.34 (d, 1 H) 7.63 (d, 1 H) 7.41 (dd, 1 H) 4.23 (t, 2 H) 2.47 (s, 3 H) 1.76 - 1.98 (m, 2 H) 0.87 (t, 3 H)
1-55	N-(2-Fluorophenyl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	($CDCl_3$) δ ppm: 8.10 (d, 1 H) 7.89 (td, 1 H) 7.84 (br. s., 1 H) 7.03 - 7.33 (m, 3 H) 4.19 (t, 2 H) 1.91 - 2.06 (m, 2 H) 1.00 (t, 3 H)
1-56	N-(2,5-Difluorophenyl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	($CDCl_3$) δ ppm: 8.08 - 8.13 (m, 1 H) 7.96 - 8.06 (m, 1 H) 7.72 (br. s., 1 H) 7.13 (ddd, 1 H) 6.65 - 6.86 (m, 1 H) 4.06 - 4.27 (m, 2 H) 1.86 - 2.09 (m, 2 H) 0.99 (t, 3 H)
1-57	N-(Benzo[d][1,3]dioxol-5-yl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	($CDCl_3$) δ ppm: 8.03 - 8.10 (m, 1 H) 7.65 - 7.80 (m, 1 H) 6.89 - 6.93 (m, 1 H) 6.85 (d, 1 H) 6.77 (dd, 1 H) 6.03 (s, 2 H) 4.10 - 4.23 (m, 2 H) 1.89 - 2.06 (m, 2 H) 0.98 (t, 3 H)

Cpd	IUPAC Name	^{1}H-NMR (300 MHz, solvent), δ ppm
1-58	N-(4-Morpholinophenyl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 10.68 (s, 1 H) 8.50 (s, 1 H) 7.50 (m, 2 H) 6.97 (m, 2 H) 4.21 (t, 2 H) 3.66 - 3.82 (m, 4 H) 2.99 - 3.15 (m, 4 H) 1.74 - 1.97 (m, 2 H) 0.86 (t, 3 H)
1-59	N-(3-Methoxyphenyl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 10.92 (br. s., 1 H) 8.52 (s, 1 H) 7.25 - 7.34 (m, 2 H) 7.13 - 7.21 (m, 1 H) 6.62 - 6.71 (m, 1 H) 4.16 - 4.28 (m, 2 H) 3.79 (s, 3 H) 1.78 - 1.94 (m, 2 H) 0.86 (t, 3 H)
1-60	3-(1-Propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-N-(3-(trifluoromethyl)phenyl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 11.26 (br. s., 1 H) 8.56 (s, 1 H) 8.34 (s, 1 H) 7.72 (d, 1 H) 7.60 (dd, 1 H) 7.39 (d, 1 H) 4.22 (t, 2 H) 1.75 - 1.95 (m, 2 H) 0.87 (t, 3 H)
1-61	N-(4-Chlorophenyl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 11.05 (br. s., 1 H) 8.58 (s, 1 H) 7.72 (m, 2 H) 7.42 (m, 2 H) 4.22 (t, 2 H) 1.78 - 1.94 (m, 2 H) 0.87 (t, 3 H)
1-62	3-(1-(Cyclopropylmethyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 12.17 (s, 1 H) 8.39 - 8.51 (m, 2 H) 7.75 - 7.91 (m, 1 H) 7.21 (d, 1 H) 6.97 - 7.14 (m, 1 H) 4.13 (d, 2 H) 1.25 - 1.45 (m, 1 H) 0.55 - 0.68 (m, 2 H) 0.35 - 0.49 (m, 2 H)
1-63	N-(Pyridin-2-yl)-3-(1-(2,2,2-trifluoroethyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 12.19 (s, 1 H) 8.58 (d, 1 H) 8.41 - 8.48 (m, 1 H) 7.80 - 7.89 (m, 1 H) 7.22 (dt, 1 H) 7.05 - 7.13 (m, 1 H) 5.30 - 5.47 (m, 2 H)
1-64	3-(3,5-Dimethyl-1-propyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine	(DMSO-d6) δ ppm: 11.97 (s, 1 H) 8.37 - 8.46 (m, 1 H) 7.76 - 7.87 (m, 1 H) 7.20 (dt, 1 H) 7.00 - 7.09 (m, 1 H) 3.90 - 4.02 (m, 2 H) 2.62 (s, 3 H) 2.45 (s, 3 H) 1.64 - 1.85 (m, 2 H) 0.86 (t, 3 H)

Cpd	IUPAC Name	^{1}H-NMR (300 MHz, solvent), δ ppm
1-65	3-(1-(Cyclopropylmethyl)-3,5-dimethyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine	($CDCl_3$) δ ppm: 9.73 (br. s., 1 H) 8.46 (ddd, 1 H) 7.65 (ddd, 1 H) 7.00 (ddd, 1 H) 6.75 - 6.83 (m, 1 H) 3.96 (d, 2 H) 2.64 (s, 3 H) 2.58 (s, 3 H) 1.17 - 1.33 (m, 1 H) 0.51 - 0.62 (m, 2 H) 0.33 - 0.44 (m, 2 H)
1-66	3-(1-(Cyclopropylmethyl)-3,5-dimethyl-1H-pyrazol-4-yl)-N-(6-methylpyridin-2-yl)-1,2,4-thiadiazol-5-amine	($CDCl_3$) δ ppm: 9.76 (br. s., 1 H) 7.52 (dd, 1 H) 6.82 (d, 1 H) 6.57 (d, 1 H) 3.95 (d, 2 H) 2.64 (s, 3 H) 2.61 (s, 3 H) 2.58 (s, 3 H) 1.17 - 1.33 (m, 1 H) 0.51 - 0.61 (m, 2 H) 0.34 - 0.42 (m, 2 H)
1-67	3-(3-Methyl-1-propyl-1H-pyrazol-4-yl)-N-(6-methylpyridin-2-yl)-1,2,4-thiadiazol-5-amine	($CDCl_3$) δ ppm: 9.73 (br. s., 1 H) 7.94 (s, 1 H) 7.54 (dd, 1 H) 6.84 (d, 1 H) 6.63 (d, 1 H) 4.03 (t, 2 H) 2.65 (s, 3 H) 2.62 (s, 3 H) 1.81 - 1.96 (m, 2 H) 0.93 (t, 3 H)
1-68	N-(6-Ethylpyridin-2-yl)-3-(3-methyl-1-propyl-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	($CDCl_3$) δ ppm: 9.49 (br. s., 1 H) 7.97 (s, 1 H) 7.61 (t, 1 H) 6.88 (d, 1 H) 6.74 (d, 1 H) 4.05 (t, 2 H) 2.91 (q, 2 H) 2.64 (s, 3 H) 1.84 - 1.99 (m, 2 H) 1.43 (t, 3 H) 0.95 (t, 3 H)
1-69	3-(3-Methyl-1-propyl-1H-pyrazol-4-yl)-N-(6-(trifluoromethyl)pyridin-2-yl)-1,2,4-thiadiazol-5-amine	($CDCl_3$) δ ppm: 7.95 (s, 1 H) 7.85 (dd, 1 H) 7.39 (d, 1 H) 7.05 (d, 1 H) 4.05 (t, 2 H) 2.65 (s, 3 H) 1.83 - 1.98 (m, 2 H) 0.94 (t, 3 H)
1-70	3-(3-Methyl-1-propyl-1H-pyrazol-4-yl)-N-(3-(trifluoromethyl)pyridin-2-yl)-1,2,4-thiadiazol-5-amine	($CDCl_3$) δ ppm: 8.90 (d, 1 H) 8.23 (br. s., 1 H) 8.01 (s, 1 H) 7.49 (d, 1 H) 6.24 (t, 1 H) 4.08 (t, 2 H) 2.67 (s, 3 H) 1.87 - 2.01 (m, 2 H) 0.97 (t, 3 H)
1-71	N-(5-Chloropyridin-2-yl)-3-(3-methyl-1-propyl-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	($CDCl_3$) δ ppm: 8.44 (dd, 1 H) 7.93 (s, 1 H) 7.60 (dd, 1 H) 6.75 (dd, 1 H) 4.04 (t, 2 H) 2.65 (s, 3 H) 1.80 - 1.97 (m, 2 H) 0.93 (t, 3 H)

Cpd	IUPAC Name	^{1}H-NMR (300 MHz, solvent), δ ppm
1-72	N-(5-Fluoropyridin-2-yl)-3-(3-methyl-1-propyl-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	($CDCl_3$) δ ppm: 10.25 (br. s., 1 H) 8.32 (d, 1 H) 7.91 (s, 1 H) 7.32 - 7.43 (m, 1 H) 6.72 (dd, 1 H) 4.02 (t, 2 H) 2.64 (s, 3 H) 1.79 - 1.94 (m, 2 H) 0.92 (t, 3 H)
1-73	6-(3-(3-Methyl-1-propyl-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-ylamino)nicotinonitrile	(DMSO-d6) δ ppm: 12.64 (br. s., 1 H) 8.92 (dd, 1 H) 8.21 (dd, 1 H) 8.10 (s, 1 H) 7.27 (dd, 1 H) 4.05 (t, 2 H) 2.50 (s, 3 H) 1.72 - 1.87 (m, 2 H) 0.84 (t, 3 H)
1-74	3-(3-Methyl-1-propyl-1H-pyrazol-4-yl)-N-(6-morpholinopyridin-2-yl)-1,2,4-thiadiazol-5-amine	($CDCl_3$) δ ppm: 9.10 (br. s., 1 H) 7.95 (s, 1 H) 7.46 - 7.55 (m, 1 H) 6.31 (d, 1 H) 6.26 (d, 1 H) 4.05 (t, 2 H) 3.84 - 3.94 (m, 4 H) 3.62 - 3.71 (m, 4 H) 2.63 (s, 3 H) 1.85 - 1.99 (m, 2 H) 0.95 (t, 3 H)
1-75	N-(6-Methoxypyridin-2-yl)-3-(3-methyl-1-propyl-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	($CDCl_3$) δ ppm: 9.24 (br. s., 1 H) 7.94 (s, 1 H) 7.56 (t, 1 H) 6.37 - 6.49 (m, 2 H) 4.18 (s, 3 H) 4.05 (t, 2 H) 2.64 (s, 3 H) 1.84 - 1.98 (m, 2 H) 0.94 (t, 3 H)
1-76	N-(6-Fluoropyridin-2-yl)-3-(3-methyl-1-propyl-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine	($CDCl_3$) δ ppm: 7.94 (s, 1 H) 7.68 - 7.81 (m, 1 H) 6.72 (dd, 1 H) 6.62 (dd, 1 H) 4.04 (t, 2 H) 2.64 (s, 3 H) 1.83 - 1.98 (m, 2 H) 0.94 (t, 3 H)
1-77	4-(1-Propyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)thiazol-2-amine	(DMSO-d6) δ ppm: 11.31 (br. s., 1 H) 8.25 - 8.34 (m, 1 H) 7.97 (s, 1 H) 7.76 (s, 1 H) 7.61 - 7.73 (m, 1 H) 7.07 (d, 1 H) 6.96 (s, 1 H) 6.86 - 6.94 (m, 1 H) 4.08 (t, 2 H) 1.72 - 1.88 (m, 2 H) 0.85 (t, 3 H)
1-78	N-(Benzo[d][1,3]dioxol-5-yl)-4-(1-propyl-1H-pyrazol-4-yl)thiazol-2-amine	(DMSO-d6) δ ppm: 10.00 (br. s., 1 H) 8.00 (s, 1 H) 7.76 (s, 1 H) 7.40 (t, 1 H) 6.99 - 7.08 (m, 1 H) 6.86 (d, 1 H) 6.81 (d, 1 H) 5.98 (s, 2 H) 4.08

Cpd	IUPAC Name	^{1}H-NMR (300 MHz, solvent), δ ppm
		(t, 2 H) 1.71 - 1.89 (m, 2 H) 0.84 (t, 3 H)
1-79	N-(2-Fluorophenyl)-4-(1-propyl-1H-pyrazol-4-yl)thiazol-2-amine	(DMSO-d6 +Na_2CO_3) δ ppm: 8.43 - 8.64 (m, 1 H), 8.03 (s, 1 H), 7.78 (s, 1 H), 7.09 - 7.34 (m, 2 H), 6.92 - 7.09 (m, 1 H), 6.88 (s, 1 H), 4.08 (t, 2 H), 1.81 (sxt, 2 H), 0.85 (t, 3 H)
1-80	4-(3-Methyl-1-propyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)thiazol-2-amine	($CDCl_3$) δ ppm: 9.28 (br. s., 1 H) 8.37 (dd, 1 H) 7.72 (s, 1 H) 7.50 - 7.58 (m, 1 H) 6.84 - 6.92 (m, 1 H) 6.74 (d, 1 H) 6.67 (s, 1 H) 3.99 (t, 2 H) 2.50 (s, 3 H) 1.76 - 1.94 (m, 2 H) 0.91 (t, 3 H)
1-81	4-(3-Methyl-1-propyl-1H-pyrazol-4-yl)-N-(6-methylpyridin-2-yl)thiazol-2-amine	($CDCl_3$) δ ppm: 9.13 (br. s., 1 H) 7.73 (s, 1 H) 7.44 (dd, 1 H) 6.74 (d, 1 H) 6.65 (s, 1 H) 6.56 (d, 1 H) 4.00 (t, 2 H) 2.56 (s, 3 H) 2.49 (s, 3 H) 1.78 - 1.93 (m, 2 H) 0.92 (t, 3 H)
1-82	N-(5-Chloropyridin-2-yl)-4-(3-methyl-1-propyl-1H-pyrazol-4-yl)thiazol-2-amine	(DMSO-d6) δ ppm: 11.39 (s, 1 H) 8.32 (d, 1 H) 7.84 (s, 1 H) 7.79 (dd, 1 H) 7.15 (d, 1 H) 6.84 (s, 1 H) 3.99 (t, 2 H) 2.36 (s, 3 H) 1.67 - 1.86 (m, 2 H) 0.83 (t, 3 H)
1-83	N-(6-Methoxypyridin-3-yl)-4-(3-methyl-1-propyl-1H-pyrazol-4-yl)thiazol-2-amine	(DMSO-d6) δ ppm: 10.04 (s, 1 H) 8.53 - 8.59 (m, 1 H) 8.00 (dd, 1 H) 7.95 (s, 1 H) 6.81 (d, 1 H) 6.67 (s, 1 H) 4.00 (t, 2 H) 3.82 (s, 3 H) 2.36 (s, 3 H) 1.71 - 1.86 (m, 2 H) 0.84 (t, 3 H)
1-84	N-(2-Methoxypyridin-3-yl)-4-(3-methyl-1-propyl-1H-pyrazol-4-yl)thiazol-2-amine	(DMSO-d6) δ ppm: 9.73 (br. s., 1 H) 8.80 - 8.91 (m, 1 H) 7.98 (s, 1 H) 7.73 (dd, 1 H) 6.99 (dd, 1 H) 6.73 (s, 1 H) 3.97 - 4.04 (m, 2 H) 3.97 (s, 3 H) 2.37 (s, 3 H) 1.70 - 1.87 (m, 2 H) 0.85 (t, 3 H)
1-85	4-(1-Propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-	(DMSO-d6) δ ppm: 11.26 (s, 1 H) 8.26 - 8.35 (m, 1 H) 8.15 - 8.20 (m, 1 H) 7.64 - 7.76 (m, 1

Cpd	IUPAC Name	^{1}H-NMR (300 MHz, solvent), δ ppm
	yl)thiazol-2-amine	H) 7.09 - 7.17 (m, 1 H) 6.88 - 6.98 (m, 2 H) 4.19 (t, 2 H) 1.73 - 1.94 (m, 2 H) 0.86 (t, 3 H)
1-86	4-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)thiazol-2-amine	(DMSO-d6) δ ppm: 11.32 (s, 1 H) 8.29 (d, 1 H) 8.02 (s, 1 H) 7.77 (s, 1 H) 7.60 - 7.74 (m, 1 H) 7.06 (d, 1 H) 6.98 (s, 1 H) 6.83 - 6.94 (m, 1 H) 3.99 (d, 2 H) 1.11 - 1.38 (m, 1 H) 0.47 - 0.69 (m, 2 H) 0.22 - 0.46 (m, 2 H)
1-87	N-(Pyridin-2-yl)-4-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)thiazol-2-amine	(DMSO-d6) δ ppm: 11.33 (br. s., 1 H) 8.25 - 8.32 (m, 1 H) 8.09 (s, 1 H) 7.93 (d, 1 H) 7.64 - 7.74 (m, 1 H) 7.04 - 7.11 (m, 2 H) 6.89 - 6.95 (m, 1 H) 5.17 (q, 2 H)
1-88	3-(3-methyl-1-propyl-1H-pyrazol-4-yl)-N-(pyridin-3-yl)-1,2,4-thiadiazol-5-amine	($CDCl_3$) δ ppm: 9.14 (s, 1H); 8.73 (d, 1H, 3Hz); 8.39 (m, 1H); 8.01 (m, 1H); 7.93 (s, 1H); 7.38 (m, 1H); 4.03 (t, 2H, 7Hz); 2.61 (s, 3H); 1.88 (m, 2H); 0.91 (t, 3H, 7.5Hz)

PHARMACOLOGY

The compounds provided in the present invention are highly selective antagonists of the human adenosine A_3 receptor. As such, the compounds of Formula I to III block the activation of adenosine A_3 receptor induced by an agonist of the receptor, while they have little or no effect against other subtypes of adenosine receptors including human A_1, human A_{2A} and human A_{2B} receptors.

Material and methods

Radioligand binding assay for the evaluation of the affinity of compounds for the human adenosine A_3 receptors:

Radioligand binding assay for the evaluation of the affinity of compounds for the human adenosine A_3 receptors expressed in transfected HEK-293 cells has been performed in 96-well plate and following the experimental conditions described in Salvatore et al. ((1993) *Proc. Natl. Acad. Sci. USA, 90: 10365*).

Briefly, cell membrane homogenates (40 μg protein) were incubated for 120 min at 22°C with 0.15 nM [^{125}I]AB-MECA in the absence or presence of the test compound in a buffer containing 50 mM Tris-HCl (pH 7.4), 5 mM $MgCl_2$, 1 mM EDTA and 2 units/ml ADA. Nonspecific binding was determined in the presence of 1 μM IB-MECA. Following incubation, the samples were filtered rapidly under vacuum through glass fiber filters (GF/B, Packard) presoaked with 0.3% PEI and rinsed several times with ice-cold 50 mM Tris-HCl using a 96-sample cell harvester (Unifilter, Packard). The filters were dried then counted for radioactivity in a scintillation counter (Topcount, Packard) using a scintillation cocktail (Microscint 0, Packard).

The results are expressed as a percent inhibition of the control radioligand specific binding. The standard reference compound is IB-MECA, which is tested in each experiment at several concentrations to obtain a competition curve from which its IC_{50} and Ki values are calculated.

The inhibition curves were generated using the Prism GraphPad program (Graph Pad Software Inc, San Diego, USA). IC_{50} and Ki determinations were extrapolated from data obtained from 3- to 8-point-concentration response curves using a non linear

regression analysis. The mean of IC_{50} and Ki obtained from at least three independent experiments of selected molecules performed in duplicate were calculated.

Compounds Nr 1-8, 1-9, 1-10, 1-12, 1-13, 1-14, 1-15, 1-19, 1-21, 1-22, 1-35, 1-42, 1-50, 1-63, 1-64 and 1-74 of the prevent invention have a Ki value on human adenosine A_3 receptors of less than 1 μM.

Radioligand binding assay for the evaluation of the affinity of compounds for the human adenosine A_1 receptors:

Radioligand binding assay for the evaluation of the affinity of compounds for the human adenosine A_1 receptors expressed in transfected HEK-293 cells has been performed in 96-well plate and following the experimental conditions described by Townsend-Nicholson and Schofield *(1994), J. Biol. Chem. 269: 2373.*

Briefly, cell membrane homogenates (20 μg protein) were incubated for 60 min at 22°C with 1 nM [^{3}H]DPCPX in the absence or presence of the test compound in a buffer containing 50 mM Tris-HCl (pH 7.4), 5 mM $MgCl_2$, 1 mM EDTA/Tris and 2 UI/ml ADA. Following incubation, the samples were filtered rapidly under vacuum through glass fiber filters (GF/B, Packard) presoaked with 0.3% PEI and rinsed several times with ice-cold 50 mM Tris-HCl using a 96-sample cell harvester (Unifilter, Packard). The filters are dried then counted for radioactivity in a scintillation counter (Topcount, Packard) using a scintillation cocktail (Microscint 0, Packard). Nonspecific binding was determined in the presence of 1 μM DPCPX.

The results are expressed as a percent inhibition of the control radioligand specific binding. The standard reference compound is DPCPX, which is tested in each experiment at several concentrations to obtain a competition curve from which its IC_{50} is calculated.

The inhibition curves were generated using the Prism GraphPad program (Graph Pad Software Inc, San Diego, USA). IC_{50} and Ki determinations were extrapolated from data obtained from 3- to 8-point-concentration response curves using a non linear regression analysis. The mean of IC_{50} and Ki obtained from at least three independent experiments of selected molecules performed in duplicate were calculated.

Compounds Nr 1-8, 1-9, 1-10, 1-12, 1-13, 1-14, 1-15, 1-19, 1-21, 1-22, 1-35, 1-42, 1-50, 1-63, 1-64 and 1-74 of the prevent invention have a Ki value on human adenosine A_1 receptors greater than 1 μM.

Radioligand binding assay for the evaluation of the affinity of compounds for the human adenosine A_{2A} receptors:

Radioligand binding assay for the evaluation of the affinity of compounds for the human adenosine A_{2A} receptors expressed in transfected HEK-293 cells has been performed in 96-well plate and following the experimental conditions described by Luthin et al ((1995) Mol. Pharmacol., 47: 307).

Briefly, cell membrane homogenates (50 μg protein) were incubated for 120 min at 22°C with 6 nM [^{3}H]CGS 21680 in the absence or presence of the test compound in a buffer containing 50 mM Tris-HCl (pH 7.4), 10 mM $MgCl_2$ and 2 UI/ml ADA. Following incubation, the samples are filtered rapidly under vacuum through glass fiber filters (GF/B, Packard) presoaked with 0.3% PEI and rinsed several times with ice-cold 50 mM Tris-HCl using a 96-sample cell harvester (Unifilter, Packard). The filters are dried then counted for radioactivity in a scintillation counter (Topcount, Packard) using a scintillation cocktail (Microscint 0, Packard). Nonspecific binding was determined in the presence of 10 μM NECA.

The results are expressed as a percent inhibition of the control radioligand specific binding. The standard reference compound is NECA, which is tested in each experiment at several concentrations to obtain a competition curve from which its IC_{50} is calculated.

The inhibition curves were generated using the Prism GraphPad program (Graph Pad Software Inc, San Diego, USA). IC_{50} and Ki determinations were extrapolated from data obtained from 3- to 8-point-concentration response curves using a non linear regression analysis. The mean of IC_{50} and Ki obtained from at least three independent experiments of selected molecules performed in duplicate were calculated.

Compounds Nr 1-8, 1-9, 1-10, 1-12, 1-13, 1-14, 1-15, 1-19, 1-21, 1-22, 1-35, 1-42, 1-50, 1-63, 1-64 and 1-74 of the prevent invention have a Ki value on human adenosine A_{2A} receptors greater than 1 μM.

Radioligand binding assay for the evaluation of the affinity of compounds for the human adenosine A_{2B} receptors:

Radioligand binding assay for the evaluation of the affinity of compounds for the human adenosine A_{2B} receptors expressed in transfected HEK-293 cells has been performed in 96-well plate and following the experimental conditions described in Stehle et al ((1992) Mol. Endocrinol. 6:384-393).

Briefly, cell membrane homogenates of HEK-293 cells (200 μg protein) were incubated for 120 min at 22°C with 0.5 nM [^{3}H]MRS1754 in the absence or presence of the test compound in a buffer containing 10 mM Hepes/Tris (pH 7.4), 1 mM $MgCl_2$ and 1 mM EDTA. Following incubation, the samples are filtered rapidly under vacuum

through glass fiber filters (GF/C, Whatman) presoaked with 0.3% PEI and rinsed several times with ice-cold 50 mM Tris-HCl using a 48-sample cell harvester (Brandel). The filters are dried then counted for radioactivity in a scintillation counter (LS series, Beckman) using a scintillation cocktail (Formula 989, Packard). Nonspecific binding is determined in the presence of 100 μM NECA.

The results are expressed as a percent inhibition of the control radioligand specific binding. The standard reference compound is NECA, which is tested in each experiment at several concentrations to obtain a competition curve from which its IC_{50} is calculated.

The inhibition curves were generated using the Prism GraphPad program (Graph Pad Software Inc, San Diego, USA). IC_{50} and Ki determinations were extrapolated from data obtained from 3- to 8-point-concentration response curves using a non linear regression analysis. The mean of IC_{50} and Ki obtained from at least three independent experiments of selected molecules performed in duplicate were calculated.

Compounds Nr 1-8, 1-9, 1-10, 1-12, 1-13, 1-14, 1-15, 1-19, 1-21, 1-22, 1-35, 1-42, 1-50, 1-63, 1-64 and 1-74 of the prevent invention have a Ki value on human adenosine A_{2B} receptors greater than 1 μM.

Luminescence-based Ca^{2+}mobilization assay for the evaluation of the antagonist properties of compounds acting at human adenosine A_3 receptors:

The functional properties of the compounds of the present invention were assessed using a cell-based Ca^{2+}-mobilization assay in which the luminescence properties of the photoprotein aequorin was directly proportional to the intracellular Ca^{2+} released within

the cell cytoplasm as it is described in literature (Detheux et al (2000) J. Exp. Med. 192:1501-1508). A CHO-K1 cell line expressing adenosine A_3AR, $G\alpha_{16}$ and mitochondrial apoaequorin were established.

In brief, cells were collected from plates with PBS containing 5 mM EDTA, pelleted, and resuspended at 7.5 x 10^5 cells/ml in DMEM-F12 medium and incubated with 5mM coelenterazine H (Molecular Probes) overnight at room temperature. Cells were then washed in DMEM-F12 medium and resuspended at a concentration of 10^5 cells/ml. For measuring an agonist activity, cells were injected to the test compounds at 8 concentrations already distributed in microtiter plate, and the light emission was recorded over 60 s using a FDSS 6000 luminometer (Hamamatsu). Then, following an incubation of 3 min, the reference agonist IB-MECA was injected at a concentration corresponding to 80 % of the maximal agonist concentration (EC_{80}) in the wells containing the cells and test compounds and the light emission was recorded over 60 s using a FDSS 6000 luminometer (Hamamatsu). Results are expressed as relative light units (RLU).

The concentration-response curves of representative compounds of the present invention were generated using the Prism GraphPad software (Graph Pad Inc, San Diego, USA). The curves were fitted to a four-parameter logistic equation:

(Y=Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*Hill Slope)

allowing determination of IC_{50} values.

Compounds Nr 1-8, 1-9, 1-14, 1-15, 1-22, 1-35, 1-50 and 1-64 of the prevent invention have an IC_{50} value on human adenosine A_3 receptors less than 1 μM.

These results demonstrate that the compounds described in the present invention have a higher affinity for human adenosine A_3 receptor as compared to others human

adenosine receptors A_1, A_{2A} and A_{2B}. Furthermore, these results show that these compounds functionally behave as antagonist of human Adenosine A_3 receptors. These compounds do not show an activity by their own but they rather block the functional activation of human adenosine A_3 receptors induced by adenosine or human A_3 receptor agonist.

Thus, the selective antagonists of human A_3 receptor provided in the present invention are expected to block the effectiveness of adenosine or A_3AR agonists at human A_3 receptor. Therefore, these selective adenosine A_3 antagonists are expected to be useful in human for the treatment of various conditions associated with dysfunction of adenosine system when adenosine A_3 receptors are overstimulated due to presence of an excess of adenosine or metabolite or endogenous ligand with human A_3AR agonist property or due to a sustained presence of these agonists in the vicinity of human A_3ARs resulting in an hyperactivation of adenosinergic system.

FORMULATION EXAMPLES

Typical examples of recipes for the formulation of the invention are as follows:

1. Tablets

Active ingredient	5 to 50 mg
Di-calcium phosphate	20 mg
Lactose	30 mg
Talcum	10 mg
Magnesium stearate	5 mg
Potato starch	ad 200 mg

In this Example, active ingredient can be replaced by the same amount of any of the compounds according to the present invention, in particular by the same amount of any of the exemplified compounds.

2. Suspension

An aqueous suspension is prepared for oral administration so that each 1 milliliter contains 1 to 5 mg of one of the active compounds, 50 mg of sodium carboxymethyl cellulose, 1 mg of sodium benzoate, 500 mg of sorbitol and water ad 1 ml.

3. Injectable

A parenteral composition is prepared by stirring 1.5 % by weight of active ingredient of the invention in 10% by volume propylene glycol and water.

4. Ointment

Active ingredient	5 to 1000 mg
Stearyl alcohol	3 g
Lanoline	5 g
White petroleum	15 g
Water	ad 100 g

5. Opthalmic solution

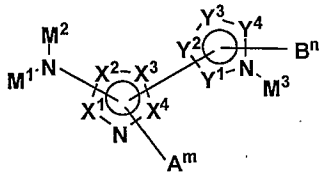
Ingredients:	Amount (wt %):
Active ingredient	0.01-2%
Hydroxypropyl methylcellulose	0.5%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide/Hydrochloric acid	For adjusting pH to 7.3-7.4
Purified water	q.s. to 100%

In this Example, active ingredient can be replaced with the same amount of any of the compounds according to the present invention, in particular by the same amount of any of the exemplified compounds.

Reasonable variations are not to be regarded as a departure from the scope of the invention. It will be obvious that the thus described invention may be varied in many ways by those skilled in the art.

CLAIMS

1. A compound according to the general Formula (I),



(I)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof, wherein:

X^1, X^2, X^3 and X^4 are each independently selected from the group of C, N, O, S and C=C representing a 5 or 6 membered heteroaryl ring which may further be substituted by 1 to 3 radicals A^m;

m is an integer ranging from 1 to 3;

A^m radicals are each independently selected from the group of hydrogen, halogen, -CN, $-CF_3$, and an optionally substituted radical selected from the group of $-(C_1-C_6)$alkyl, $-(C_1-C_6)$alkylhalo, $-(C_3-C_7)$cycloalkyl, $-(C_1-C_6)$alkylcyano, $-(C_1-C_6)$alkylheteroaryl, $-(C_1-C_6)$alkylaryl, aryl, heteroaryl, heterocycle, $-(C_0-C_6)$alkyl-OR^1, $-O-(C_2-C_6)$alkyl-OR^1, $-NR^1(C_2-C_6)$alkyl-OR^2, $-(C_3-C_7)$cycloalkyl-(C_1-C_6)alkyl, $-O-(C_3-C_7)$cycloalkyl-(C_1-C_6)alkyl, $-NR^1-(C_3-C_7)$cycloalkyl-(C_1-C_6)alkyl, $-(C_1-C_6)$alkylhalo-OR^1, $-(C_1-C_6)$alkylhalo-NR^1R^2, $-(C_0-C_6)$alkyl-S-R^1, $-O-(C_2-C_6)$alkyl-S-R^1, $-NR^1-(C_2-C_6)$alkyl-S-R^2, $-(C_0-C_6)$alkyl-S(=O)-R^1, $-O-(C_1-C_6)$alkyl-S(=O)-R^1, $-NR^1-(C_1-C_6)$alkyl-S(=O)-R^2, $-(C_0-C_6)$alkyl-$S(=O)_2-R^1$, $-O-(C_1-C_6)$alkyl-$S(=O)_2-R^1$, $-NR^1-(C_1-C_6)$alkyl-$S(=O)_2-R^2$, $-(C_0-C_6)$alkyl-NR^1R^2, $-O-(C_2-C_6)$alkyl-NR^1R^2, $-NR^1-(C_2-C_6)$alkyl-NR^2R^3, $-(C_0-C_6)$alkyl-$S(=O)_2NR^1R^2$, $-O-(C_1-C_6)$alkyl-$S(=O)_2NR^1R^2$, $-NR^1-(C_1-C_6)$alkyl-$S(=O)_2NR^2R^3$, $-(C_0-C_6)$alkyl-$NR^1-S(=O)_2R^2$, $-O-(C_2-C_6)$alkyl-$NR^1-S(=O)_2R^2$, $-NR^1-(C_2-C_6)$alkyl-$NR^2-S(=O)_2R^3$, $-(C_0-C_6)$alkyl-$C(=O)-NR^1R^2$, $-O-(C_1-C_6)$alkyl-$C(=O)-NR^1R^2$, $-NR^1-$

$(C_1\text{-}C_6)$alkyl-C(=O)-NR^2R^3, -$(C_0\text{-}C_6)$alkyl-NR^1C(=O)-R^2, -O-$(C_2\text{-}C_6)$alkyl-NR^1C(=O)-R^2, -NR^1-$(C_2\text{-}C_6)$alkyl-NR^2C(=O)-R^3, -O-$(C_2\text{-}C_6)$alkyl-OC(=O)-R^1, -NR^1-$(C_2\text{-}C_6)$alkyl-OC(=O)-R^2, -$(C_0\text{-}C_6)$alkyl-C(=O)-OR^1, -O-$(C_1\text{-}C_6)$alkyl-C(=O)-OR^1, -NR^1-$(C_1\text{-}C_6)$alkyl-C(=O)-OR^2, -$(C_0\text{-}C_6)$alkyl-C(=O)-R^1, -O-$(C_1\text{-}C_6)$alkyl-C(=O)-R^1, -NR^1-$(C_1\text{-}C_6)$alkyl-C(=O)-R^2, -$(C_0\text{-}C_6)$alkyl-NR^1-C(=O)-OR^2, -$(C_0\text{-}C_6)$alkyl-NR^1-C(=O)-NR^2R^3, -O-$(C_2\text{-}C_6)$alkyl-NR^1-C(=O)-NR^2R^3, and -NR^1-$(C_2\text{-}C_6)$alkyl-NR^2-C(=O)-NR^3R^4;

Any two radicals of A^m (A^1 and A^2) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

R^1, R^2, R^3 and R^4 are each independently hydrogen or an optionally substituted radical selected from the group of -$(C_1\text{-}C_6)$alkylhalo, -$(C_1\text{-}C_6)$alkyl, -$(C_1\text{-}C_6)$alkylcyano, -$(C_3\text{-}C_7)$cycloalkyl, -$(C_4\text{-}C_{10})$alkylcycloalkyl, heteroaryl, -$(C_1\text{-}C_6)$alkylheteroaryl, aryl, heterocycle and -$(C_1\text{-}C_6)$alkylaryl;

Any two radicals of R (R^1, R^2, R^3 or R^4) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

Y^1, Y^2, Y^3 and Y^4 are each independently selected from the group of C and N representing 5 membered heteroaryl ring which may further be substituted by 1 to 3 radicals B^n;

n is an integer ranging from 1 to 3;

B^n radicals are each independently selected from the group of hydrogen, halogen, -CN, $-CF_3$, and an optionally substituted radical selected from the group of -$(C_1\text{-}C_6)$alkyl, -$(C_1\text{-}C_6)$alkylhalo, -$(C_3\text{-}C_7)$cycloalkyl, -$(C_1\text{-}C_6)$alkylcyano, -$(C_1\text{-}C_6)$alkylheteroaryl, -$(C_1\text{-}C_6)$alkylaryl, aryl, heteroaryl, heterocycle, -$(C_0\text{-}C_6)$alkyl-OR^5, -O-$(C_2\text{-}C_6)$alkyl-OR^5, -$NR^5$$(C_2\text{-}C_6)$alkyl-$OR^6$, -$(C_3\text{-}C_7)$cycloalkyl-$(C_1\text{-}C_6)$alkyl, -O-$(C_3\text{-}C_7)$cycloalkyl-$(C_1\text{-}C_6)$alkyl, -$NR^5$-$(C_3\text{-}C_7)$cycloalkyl-$(C_1\text{-}$

C_6)alkyl, -(C_1-C_6)alkylhalo-OR^5, -(C_1-C_6)alkylhalo-NR^5R^6, -(C_0-C_6)alkyl-S-R^5, -O-(C_2-C_6)alkyl-S-R^5, -NR^5-(C_2-C_6)alkyl-S-R^6, -(C_0-C_6)alkyl-S(=O)-R^5, -O-(C_1-C_6)alkyl-S(=O)-R^5, -NR^5-(C_1-C_6)alkyl-S(=O)-R^6, -(C_0-C_6)alkyl-$S(=O)_2$-R^5, -O-(C_1-C_6)alkyl-$S(=O)_2$-R^5, -NR^5-(C_1-C_6)alkyl-$S(=O)_2$-R^6, -(C_0-C_6)alkyl-NR^5R^6, -O-(C_2-C_6)alkyl-NR^5R^6, -NR^5-(C_2-C_6)alkyl-NR^6R^7, -(C_0-C_6)alkyl-$S(=O)_2NR^5R^6$, -O-(C_1-C_6)alkyl-$S(=O)_2NR^5R^6$, -NR^5-(C_1-C_6)alkyl-$S(=O)_2NR^6R^7$, -(C_0-C_6)alkyl-NR^5-$S(=O)_2R^6$, -O-(C_2-C_6)alkyl-NR^5-$S(=O)_2R^6$, -NR^5-(C_2-C_6)alkyl-NR^6-$S(=O)_2R^7$, -(C_0-C_6)alkyl-C(=O)-NR^5R^6, -O-(C_1-C_6)alkyl-C(=O)-NR^5R^6, -NR^5-(C_1-C_6)alkyl-C(=O)-NR^6R^7, -(C_0-C_6)alkyl-NR^5C(=O)-R^6, -O-(C_2-C_6)alkyl-NR^5C(=O)-R^6, -NR^5-(C_2-C_6)alkyl-NR^6C(=O)-R^7, -O-(C_2-C_6)alkyl-OC(=O)-R^5, -NR^5-(C_2-C_6)alkyl-OC(=O)-R^6, -(C_0-C_6)alkyl-C(=O)-OR^5, -O-(C_1-C_6)alkyl-C(=O)-OR^5, -NR^5-(C_1-C_6)alkyl-C(=O)-OR^6, -(C_0-C_6)alkyl-C(=O)-R^5, -O-(C_1-C_6)alkyl-C(=O)-R^5, -NR^5-(C_1-C_6)alkyl-C(=O)-R^6, -(C_0-C_6)alkyl-NR^5-C(=O)-OR^6, -(C_0-C_6)alkyl-NR^5-C(=O)-NR^6R^7, -O-(C_2-C_6)alkyl-NR^5-C(=O)-NR^6R^7 and -NR^5-(C_2-C_6)alkyl-NR^6-C(=O)-NR^7R^8;

Any two radicals of B^n (B^1 and B^2) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

R^5, R^6, R^7 and R^8 are each independently hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)alkylcyano, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl;

Any two radicals of R (R^5, R^6, R^7 or R^8) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

M^1 is selected from an optionally substituted 3 to 10 membered ring selected from the group of aryl, heteroaryl, heterocyclic and cycloalkyl;

M^2 is selected from the group of a hydrogen or an optionally substituted radical selected from the group of -(C_0-C_6)alkyl-R^9, -(C_1-C_6)alkylhalo, -(C_2-C_6)alkyl-

NR^9R^{10}, -$(C_2$-$C_6)$alkyl-OR^9, -$(C_2$-$C_6)$alkyl-SR^9, -$(C_0$-$C_6)$alkyl-C(=O)-R^9, -$(C_2$-$C_6)$alkyl-S(O)-R^9, -$(C_0$-$C_6)$alkyl-C(=O)NR^9R^{10} and -$(C_0$-$C_6)$alkyl-$S(O)_2$-R^9;

R^9 and R^{10} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of -$(C_1$-$C_6)$alkylhalo, -$(C_1$-$C_6)$alkyl, -$(C_1$-$C_6)$alkylcyano, -$(C_3$-$C_7)$cycloalkyl, -$(C_4$-$C_{10})$alkylcycloalkyl, heteroaryl, -$(C_1$-$C_6)$alkylheteroaryl, aryl, heterocycle and -$(C_1$-$C_6)$alkylaryl;

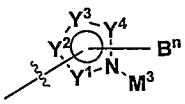
M^3 is an optionally substituted radical selected from the group of -$(C_0$-$C_6)$alkyl-R^{11}, -$(C_1$-$C_6)$alkylhalo, -$(C_2$-$C_6)$alkyl-$NR^{11}R^{12}$, -$(C_2$-$C_6)$alkyl-OR^{11} and -$(C_2$-$C_6)$alkyl-SR^{11}; and

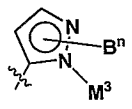
R^{11} and R^{12} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of -$(C_1$-$C_6)$alkylhalo, -$(C_1$-$C_6)$alkyl, -$(C_1$-$C_6)$alkylcyano, -$(C_3$-$C_7)$cycloalkyl, -$(C_4$-$C_{10})$alkylcycloalkyl, heteroaryl, -$(C_1$-$C_6)$alkylheteroaryl, aryl, heterocycle and -$(C_1$-$C_6)$alkylaryl;

provided that according to proviso (i):

when M^3 is -(C_0)-R^{11} (that is when M^3 is -R^{11}), then R^{11} is not H;

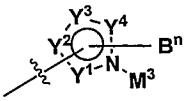
and provided that according to proviso (ii):



can not be


;

and provided that according to proviso (iii):

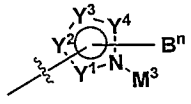
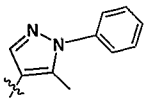
when M^1 is aryl, M^2 is H, X^1 is C, X^2 is C, X^3 is C, X^4 is N, then


is not linked to X^2;

and provided that according to proviso (iv):

A^1 and A^2 radicals are not linked to form an imidazopyridazinyl ring;

and provided that according to proviso (v):

when  is  and linked to X^4, X^1 is C, X^2 is S, X^3 is C, X^4 is C, n is 1, A^1 is H, Y^1, Y^2, Y^3 are C, Y^4 is N, then M^1 can not be an optionally substituted aryl, 1-methyl-1H-indazol-4-yl, 1H-indazol-3-yl and 1H-indazol-4-yl;

and provided that according to proviso (vi):

when M^3 is 4-methylphenyl, then B^n can not be a phenyl;

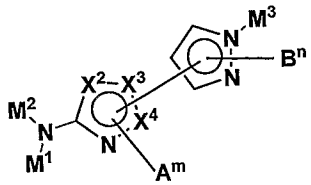
and provided that according to proviso (vii):

when M^1M^2N is linked to X^1, and X^1 is C, X^2 is S, X^3 is C, X^4 is C, to provide a thiazole ring, n is 1, then A^1 is not a pyridyl;

and provided that according to proviso (viii):

when M^1M^2N is linked to X^1, and X^1 is C, X^2 is S, X^3 is C, X^4 is C, to provide a thiazole ring, n is 1, then A^1 is not an optionally substituted imidazolyl or triazolyl ring.

2. A compound according to claim 1 having the Formula (II),



(II)

X^2, X^3 and X^4 are each independently selected from the group of C, N, O, S and C=C representing a 5 or 6 membered heteroaryl ring which may further be substituted by 1 to 3 radicals A^m;

m is an integer ranging from 1 to 3;

A^m radicals are each independently selected from the group of hydrogen, halogen, -CN, -CF_3, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_3-C_7)cycloalkyl, -(C_3-C_8)cycloalkenyl, -(C_1-C_6)alkylcyano, -(C_1-C_6)alkylheteroaryl, -(C_1-C_6)alkylaryl, aryl, heteroaryl, heterocycle, -(C_0-C_6)alkyl-OR^1, -NR^1(C_2-C_6)alkyl-OR^2, -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -O-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -NR^1-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo-OR^1, -(C_1-C_6)alkylhalo-NR^1R^2, -(C_0-C_6)alkyl-S-R^1, -NR^1-(C_2-C_6)alkyl-S-R^2, -(C_0-C_6)alkyl-S(=O)-R^1, -NR^1-(C_1-C_6)alkyl-S(=O)-R^2, -(C_0-C_6)alkyl-$S(=O)_2$-R^1, -NR^1-(C_1-C_6)alkyl-$S(=O)_2$-R^2, -(C_0-C_6)alkyl-NR^1R^2, -NR^1-(C_2-C_6)alkyl-NR^2R^3, -(C_0-C_6)alkyl-$S(=O)_2NR^1R^2$, -NR^1-(C_1-C_6)alkyl-$S(=O)_2NR^2R^3$, -(C_0-C_6)alkyl-NR^1-$S(=O)_2R^2$, -NR^1-(C_2-C_6)alkyl-NR^2-$S(=O)_2R^3$, -(C_0-C_6)alkyl-C(=O)-NR^1R^2, -NR^1-(C_1-C_6)alkyl-C(=O)-NR^2R^3, -(C_0-C_6)alkyl-NR^1C(=O)-R^2, -NR^1-(C_2-C_6)alkyl-NR^2C(=O)-R^3, -NR^1-(C_2-C_6)alkyl-OC(=O)-R^2, -(C_0-C_6)alkyl-C(=O)-OR^1, -NR^1-(C_1-C_6)alkyl-C(=O)-OR^2, -(C_0-C_6)alkyl-C(=O)-R^1, -NR^1-(C_1-C_6)alkyl-C(=O)-R^2, -(C_0-C_6)alkyl-NR^1-C(=O)-OR^2, -(C_0-C_6)alkyl-NR^1-C(=O)-NR^2R^3, and -NR^1-(C_2-C_6)alkyl-NR^2-C(=O)-NR^3R^4;

Any two radicals of A^m (A^1 and A^2) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

R^1, R^2, R^3 and R^4 are each independently hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)alkylcyano, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl;

Any two radicals of R (R^1, R^2, R^3 or R^4) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

n is an integer ranging from 1 to 2;

B^n radicals are each independently selected from the group of hydrogen, halogen, -CN, -CF_3, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylcyano, -(C_1-C_6)alkylheteroaryl, -(C_1-C_6)alkylaryl, aryl, heteroaryl, heterocycle, -(C_0-C_6)alkyl-

OR^5; -O-$(C_2$-$C_6)$alkyl-OR^5, -$NR^5(C_2$-$C_6)$alkyl-OR^6, -$(C_3$-$C_7)$cycloalkyl-$(C_1$-$C_6)$alkyl, -O-$(C_3$-$C_7)$cycloalkyl-$(C_1$-$C_6)$alkyl, -NR^5-$(C_3$-$C_7)$cycloalkyl-$(C_1$-$C_6)$alkyl, -$(C_1$-$C_6)$alkylhalo-OR^5, -$(C_1$-$C_6)$alkylhalo-NR^5R^6, -$(C_0$-$C_6)$alkyl-S-R^5, -O-$(C_2$-$C_6)$alkyl-S-R^5, -NR^5-$(C_2$-$C_6)$alkyl-S-R^6, -$(C_0$-$C_6)$alkyl-S(=O)-R^5, -O-$(C_1$-$C_6)$alkyl-S(=O)-R^5, -NR^5-$(C_1$-$C_6)$alkyl-S(=O)-R^6, -$(C_0$-$C_6)$alkyl-$S(=O)_2$-R^5, -O-$(C_1$-$C_6)$alkyl-$S(=O)_2$-R^5, -NR^5-$(C_1$-$C_6)$alkyl-$S(=O)_2$-R^6, -$(C_0$-$C_6)$alkyl-NR^5R^6, -O-$(C_2$-$C_6)$alkyl-NR^5R^6, -NR^5-$(C_2$-$C_6)$alkyl-NR^6R^7, -$(C_0$-$C_6)$alkyl-$S(=O)_2NR^5R^6$, -O-$(C_1$-$C_6)$alkyl-$S(=O)_2NR^5R^6$, -NR^5-$(C_1$-$C_6)$alkyl-$S(=O)_2NR^6R^7$, -$(C_0$-$C_6)$alkyl-NR^5-$S(=O)_2R^6$, -O-$(C_2$-$C_6)$alkyl-NR^5-$S(=O)_2R^6$, -NR^5-$(C_2$-$C_6)$alkyl-NR^6-$S(=O)_2R^7$, -$(C_0$-$C_6)$alkyl-C(=O)-NR^5R^6, -O-$(C_1$-$C_6)$alkyl-C(=O)-NR^5R^6, -NR^5-$(C_1$-$C_6)$alkyl-C(=O)-NR^6R^7, -$(C_0$-$C_6)$alkyl-NR^5C(=O)-R^6, -O-$(C_2$-$C_6)$alkyl-NR^5C(=O)-R^6, -NR^5-$(C_2$-$C_6)$alkyl-NR^6C(=O)-R^7, -O-$(C_2$-$C_6)$alkyl-OC(=O)-R^5, -NR^5-$(C_2$-$C_6)$alkyl-OC(=O)-R^6, -$(C_0$-$C_6)$alkyl-C(=O)-OR^5, -O-$(C_1$-$C_6)$alkyl-C(=O)-OR^5, -NR^5-$(C_1$-$C_6)$alkyl-C(=O)-OR^6, -$(C_0$-$C_6)$alkyl-C(=O)-R^5, -O-$(C_1$-$C_6)$alkyl-C(=O)-R^5, -NR^5-$(C_1$-$C_6)$alkyl-C(=O)-R^6, -$(C_0$-$C_6)$alkyl-NR^5-C(=O)-OR^6, -$(C_0$-$C_6)$alkyl-NR^5-C(=O)-NR^6R^7, -O-$(C_2$-$C_6)$alkyl-NR^5-C(=O)-NR^6R^7 and -NR^5-$(C_2$-$C_6)$alkyl-NR^6-C(=O)-NR^7R^8;

R^5, R^6, R^7 and R^8 are each independently hydrogen or an optionally substituted radical selected from the group of -$(C_1$-$C_6)$alkylhalo, -$(C_1$-$C_6)$alkyl, -$(C_1$-$C_6)$alkylcyano, -$(C_3$-$C_7)$cycloalkyl, -$(C_4$-$C_{10})$alkylcycloalkyl, heteroaryl, -$(C_1$-$C_6)$alkylheteroaryl, aryl, heterocycle and -$(C_1$-$C_6)$alkylaryl;

Any two radicals of R (R^5, R^6, R^7 or R^8) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

M^1 is selected from an optionally substituted 3 to 10 membered ring selected from the group of aryl, heteroaryl, heterocyclic and cycloalkyl;

M^2 is selected from the group of a hydrogen or an optionally substituted radical selected from the group of -$(C_0$-$C_6)$alkyl-R^9, -$(C_1$-$C_6)$alkylhalo, -$(C_2$-$C_6)$alkyl-

NR^9R^{10}, -(C_2-C_6)alkyl-OR^9, -(C_2-C_6)alkyl-SR^9, -(C_0-C_6)alkyl-C(=O)-R^9, -(C_2-C_6)alkyl-S(O)-R^9, -(C_0-C_6)alkyl-C(=O)NR^9R^{10} and -(C_0-C_6)alkyl-$S(O)_2$-R^9;

R^9 and R^{10} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)alkylcyano, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl;

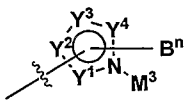
M^3 is an optionally substituted radical selected from the group of -(C_3-C_7)cycloalkyl, aryl, heteroaryl, heterocycle, -(C_1-C_6)alkyl-R^{11}, -(C_1-C_6)alkylhalo, -(C_2-C_6)alkyl-$NR^{11}R^{12}$, -(C_2-C_6)alkyl-OR^{11} and -(C_2-C_6)alkyl-SR^{11}; and

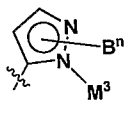
R^{11} and R^{12} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)alkylcyano, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl;

provided that according to proviso (i):

when M^3 is -(C_0)-R^{11} (that is when M^3 is -R^{11}), then R^{11} is not H;

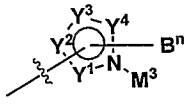
and provided that according to proviso (ii):



can not be


;

and provided that according to proviso (iii):

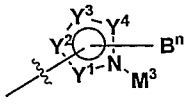
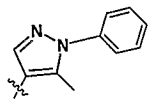
when M^1 is aryl, M^2 is H, X^2 is C, X^3 is C, X^4 is N, then


is not linked to X^2;

and provided that according to proviso (iv):

A^1 and A^2 radicals are not linked to form an imidazopyridazinyl ring;

and provided that according to proviso (v):

when  is  and linked to X^4, X^2 is S, X^3 is C, X^4 is C, n is 1, A^1 is H, then M^1 can not be an optionally substituted aryl, 1-methyl-1H-indazol-4-yl, 1H-indazol-3-yl and 1H-indazol-4-yl;

and provided that according to proviso (vi):

when M^3 is 4-methylphenyl, then B^n can not be a phenyl;

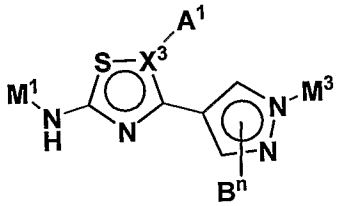
and provided that according to proviso (vii):

when X^2 is S, X^3 is C, X^4 is C, n is 1, then A^1 when linked to either X^3 or X^4 is not a pyridyl;

and provided that according to proviso (viii):

when X^2 is S, X^3 is C, X^4 is C, to provide a thiazole ring, n is 1, then A^1 is not an optionally substituted imidazolyl or triazolyl ring.

3. A compound according to claim 2 having the Formula (III),



(III)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof, wherein:

X^3 is selected from C or N which may further be substituted by A^1;

A^1 radicals are each independently selected from the group of hydrogen, halogen, -CN, $-CF_3$, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylcyano, -(C_1-

C_6)alkylheteroaryl, -(C_1-C_6)alkylaryl, heterocycle, -(C_0-C_6)alkyl-OR^1, -NR^1(C_2-C_6)alkyl-OR^2, -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -O-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -NR^1-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo-OR^1, -(C_1-C_6)alkylhalo-NR^1R^2, -NR^1-(C_2-C_6)alkyl-S-R^2, -(C_0-C_6)alkyl-S(=O)-R^1, -NR^1-(C_1-C_6)alkyl-S(=O)-R^2, -(C_0-C_6)alkyl-$S(=O)_2$-R^1, -NR^1-(C_1-C_6)alkyl-$S(=O)_2$-R^2, -(C_0-C_6)alkyl-NR^1R^2, -NR^1-(C_2-C_6)alkyl-NR^2R^3, -(C_0-C_6)alkyl-$S(=O)_2NR^1R^2$, -NR^1-(C_1-C_6)alkyl-$S(=O)_2NR^2R^3$, -(C_0-C_6)alkyl-NR^1-$S(=O)_2R^2$, -NR^1-(C_2-C_6)alkyl-NR^2-$S(=O)_2R^3$, -(C_0-C_6)alkyl-C(=O)-NR^1R^2, -NR^1-(C_1-C_6)alkyl-C(=O)-NR^2R^3, -(C_0-C_6)alkyl-NR^1C(=O)-R^2, -NR^1-(C_2-C_6)alkyl-NR^2C(=O)-R^3, -NR^1-(C_2-C_6)alkyl-OC(=O)-R^2, -(C_0-C_6)alkyl-C(=O)-OR^1, -NR^1-(C_1-C_6)alkyl-C(=O)-OR^2, -(C_0-C_6)alkyl-C(=O)-R^1, -NR^1-(C_1-C_6)alkyl-C(=O)-R^2, -(C_0-C_6)alkyl-NR^1-C(=O)-OR^2, -(C_0-C_6)alkyl-NR^1-C(=O)-NR^2R^3, and -NR^1-(C_2-C_6)alkyl-NR^2-C(=O)-NR^3R^4;

R^1, R^2, R^3 and R^4 are each independently hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)alkylcyano, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl;

Any two radicals of R (R^1, R^2, R^3 or R^4) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

n is an integer ranging from 1 to 2;

B^n radicals are each independently selected from the group of hydrogen, halogen, -CN, -CF_3, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylcyano, -(C_1-C_6)alkylheteroaryl, -(C_1-C_6)alkylaryl, aryl, heteroaryl, heterocycle, -(C_0-C_6)alkyl-OR^5, -O-(C_2-C_6)alkyl-OR^5, -NR^5(C_2-C_6)alkyl-OR^6, -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -O-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -NR^5-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo-OR^5, -(C_1-C_6)alkylhalo-NR^5R^6, -(C_0-C_6)alkyl-S-R^5, -O-(C_2-C_6)alkyl-S-R^5, -NR^5-(C_2-C_6)alkyl-S-R^6, -(C_0-C_6)alkyl-S(=O)-R^5, -O-(C_1-C_6)alkyl-S(=O)-R^5, -NR^5-(C_1-C_6)alkyl-S(=O)-R^6, -(C_0-C_6)alkyl-$S(=O)_2$-R^5, -O-

$(C_1\text{-}C_6)$alkyl-$S(=O)_2$-R^5, -NR^5-$(C_1\text{-}C_6)$alkyl-$S(=O)_2$-R^6, -$(C_0\text{-}C_6)$alkyl-NR^5R^6, -O-$(C_2\text{-}C_6)$alkyl-NR^5R^6, -NR^5-$(C_2\text{-}C_6)$alkyl-NR^6R^7, -$(C_0\text{-}C_6)$alkyl-$S(=O)_2NR^5R^6$, -O-$(C_1\text{-}C_6)$alkyl-$S(=O)_2NR^5R^6$, -NR^5-$(C_1\text{-}C_6)$alkyl-$S(=O)_2NR^6R^7$, -$(C_0\text{-}C_6)$alkyl-NR^5-$S(=O)_2R^6$, -O-$(C_2\text{-}C_6)$alkyl-NR^5-$S(=O)_2R^6$, -NR^5-$(C_2\text{-}C_6)$alkyl-NR^6-$S(=O)_2R^7$, -$(C_0\text{-}C_6)$alkyl-C(=O)-NR^5R^6, -O-$(C_1\text{-}C_6)$alkyl-C(=O)-NR^5R^6, -NR^5-$(C_1\text{-}C_6)$alkyl-C(=O)-NR^6R^7, -$(C_0\text{-}C_6)$alkyl-NR^5C(=O)-R^6, -O-$(C_2\text{-}C_6)$alkyl-NR^5C(=O)-R^6, -NR^5-$(C_2\text{-}C_6)$alkyl-NR^6C(=O)-R^7, -O-$(C_2\text{-}C_6)$alkyl-OC(=O)-R^5, -NR^5-$(C_2\text{-}C_6)$alkyl-OC(=O)-R^6, -$(C_0\text{-}C_6)$alkyl-C(=O)-OR^5, -O-$(C_1\text{-}C_6)$alkyl-C(=O)-OR^5, -NR^5-$(C_1\text{-}C_6)$alkyl-C(=O)-OR^6, -$(C_0\text{-}C_6)$alkyl-C(=O)-R^5, -O-$(C_1\text{-}C_6)$alkyl-C(=O)-R^5, -NR^5-$(C_1\text{-}C_6)$alkyl-C(=O)-R^6, -$(C_0\text{-}C_6)$alkyl-NR^5-C(=O)-OR^6, -$(C_0\text{-}C_6)$alkyl-NR^5-C(=O)-NR^6R^7, -O-$(C_2\text{-}C_6)$alkyl-NR^5-C(=O)-NR^6R^7 and -NR^5-$(C_2\text{-}C_6)$alkyl-NR^6-C(=O)-NR^7R^8;

R^5, R^6, R^7 and R^8 are each independently hydrogen or an optionally substituted radical selected from the group of -$(C_1\text{-}C_6)$alkylhalo, -$(C_1\text{-}C_6)$alkyl, -$(C_1\text{-}C_6)$alkylcyano, -$(C_3\text{-}C_7)$cycloalkyl, -$(C_4\text{-}C_{10})$alkylcycloalkyl, heteroaryl, -$(C_1\text{-}C_6)$alkylheteroaryl, aryl, heterocycle and -$(C_1\text{-}C_6)$alkylaryl;

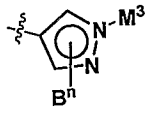
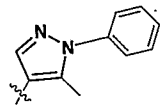
Any two radicals of R (R^5, R^6, R^7 or R^8) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

M^1 is selected from an optionally substituted aryl and heteroaryl;

M^3 is an optionally substituted radical selected from the group of -$(C_3\text{-}C_7)$cycloalkyl, aryl, heteroaryl, heterocycle, -$(C_1\text{-}C_6)$alkyl-R^{11}, -$(C_1\text{-}C_6)$alkylhalo, -$(C_2\text{-}C_6)$alkyl-$NR^{11}R^{12}$, -$(C_2\text{-}C_6)$alkyl-OR^{11} and -$(C_2\text{-}C_6)$alkyl-SR^{11}; and

R^{11} and R^{12} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of -$(C_1\text{-}C_6)$alkylhalo, -$(C_1\text{-}C_6)$alkyl, -$(C_1\text{-}C_6)$alkylcyano, -$(C_3\text{-}C_7)$cycloalkyl, -$(C_4\text{-}C_{10})$alkylcycloalkyl, heteroaryl, -$(C_1\text{-}C_6)$alkylheteroaryl, aryl, heterocycle and -$(C_1\text{-}C_6)$alkylaryl;

and provided that according to proviso (v):

when  is  , X^3 is C, n is 1, A^1 is H, then M^1 can not be an optionally substituted aryl, 1-methyl-1H-indazol-4-yl, 1H-indazol-3-yl and 1H-indazol-4-yl;

and provided that according to proviso (vi):

when M^3 is 4-methylphenyl, then B^n can not be a phenyl;

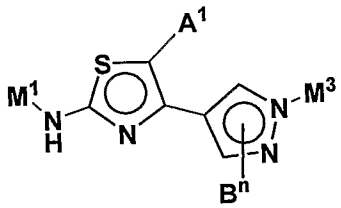
and provided that according to proviso (vii):

A^1 is different from a pyridyl;

and provided that according to proviso (viii):

when X^3 is C, to provide a thiazole ring, n is 1, then A^1 is not an optionally substituted imidazolyl or triazolyl ring.

4. A compound according to claim 3 having the Formula (IIIA),



(IIIA)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof, wherein:

A^1 radical is selected from the group of hydrogen, halogen, -CN, $-CF_3$, and an optionally substituted radical selected from the group of $-(C_1-C_6)$alkyl, $-(C_1-C_6)$alkylhalo, $-(C_3-C_7)$cycloalkyl, $-(C_1-C_6)$alkylcyano, heterocycle, $-(C_0-C_6)$alkyl-OR^1, $-(C_3-C_7)$cycloalkyl-(C_1-C_6)alkyl, $-NR^1-(C_3-C_7)$cycloalkyl-(C_1-C_6)alkyl, $-(C_1-C_6)$alkylhalo-OR^1, $-(C_1-C_6)$alkylhalo-NR^1R^2, (C_0-C_6)alkyl-NR^1R^2, $-NR^1-(C_2-$

C_6)alkyl-NR^2R^3, -(C_0-C_6)alkyl-C(=O)-NR^1R^2, -NR^1-(C_1-C_6)alkyl-C(=O)-NR^2R^3, -(C_0-C_6)alkyl-NR^1C(=O)-R^2, -NR^1-(C_2-C_6)alkyl-NR^2C(=O)-R^3, -(C_0-C_6)alkyl-C(=O)-R^1, and -NR^1-(C_1-C_6)alkyl-C(=O)-R^2;

R^1, R^2 and R^3 are each independently hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)alkylcyano, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl;

Any two radicals of R (R^1, R^2 or R^3) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

n is an integer ranging from 1 to 2;

B^n radicals are each independently selected from the group of hydrogen, halogen, -CN, -CF_3, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_3-C_7)cycloalkyl, aryl, heteroaryl, heterocycle, -(C_0-C_6)alkyl-OR^5, -O-(C_2-C_6)alkyl-OR^5, -NR^5(C_2-C_6)alkyl-OR^6, -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -O-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -NR^5-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo-OR^5, -(C_1-C_6)alkylhalo-NR^5R^6, -(C_0-C_6)alkyl-NR^5R^6, -O-(C_2-C_6)alkyl-NR^5R^6, -NR^5-(C_2-C_6)alkyl-NR^6R^7, -(C_0-C_6)alkyl-C(=O)-NR^5R^6, -O-(C_1-C_6)alkyl-C(=O)-NR^5R^6, -(C_1-C_6)alkyl-OC(=O)-R^5, -(C_0-C_6)alkyl-C(=O)-OR^5, -O-(C_1-C_6)alkyl-C(=O)-OR^5, -NR^5-(C_1-C_6)alkyl-C(=O)-OR^6, -(C_0-C_6)alkyl-C(=O)-R^5, -O-(C_1-C_6)alkyl-C(=O)-R^5 and -NR^5-(C_1-C_6)alkyl-C(=O)-R^6;

R^5, R^6 and R^7 are each independently hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)alkylcyano, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl;

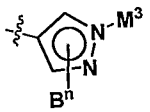
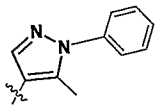
Any two radicals of R (R^5, R^6, or R^7) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

M^1 is selected from an optionally substituted aryl and heteroaryl;

M^3 is an optionally substituted radical selected from the group of -(C_3-C_7)cycloalkyl, aryl, heteroaryl, heterocycle, -(C_1-C_6)alkyl-R^{11}, -(C_1-C_6)alkylhalo, -(C_2-C_6)alkyl-$NR^{11}R^{12}$, -(C_2-C_6)alkyl-OR^{11} and -(C_2-C_6)alkyl-SR^{11};

R^{11} and R^{12} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl;

provided that according to proviso (v):

when  is  , X^3 is C, n is 1, A^1 is H, then M^1 can not be an optionally substituted aryl, 1-methyl-1H-indazol-4-yl, 1H-indazol-3-yl and 1H-indazol-4-yl;

and provided that according to proviso (vi):

when M^3 is 4-methylphenyl, then B^n can not be a phenyl;

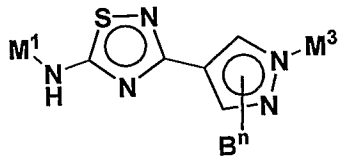
and provided that according to proviso (vii):

A^1 is not a pyridyl;

and provided that according to proviso (viii):

when X^3 is C to provide a thiazole ring, n is 1, then A^1 is not an optionally substituted imidazolyl or triazolyl ring.

5. A compound according to claim 3 having the Formula (IIIB),



(IIIB)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof, wherein:

n is an integer ranging from 1 to 2;

B^n radicals are each independently selected from the group of hydrogen, halogen, -CN, $-CF_3$, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_3-C_7)cycloalkyl, aryl, heteroaryl, heterocycle, -(C_0-C_6)alkyl-OR^5, -O-(C_2-C_6)alkyl-OR^5, -NR^5(C_2-C_6)alkyl-OR^6, -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -O-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -NR^5-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo-OR^5, -(C_1-C_6)alkylhalo-NR^5R^6, -(C_0-C_6)alkyl-NR^5R^6, -O-(C_2-C_6)alkyl-NR^5R^6, -NR^5-(C_2-C_6)alkyl-NR^6R^7, -(C_0-C_6)alkyl-C(=O)-NR^5R^6, -O-(C_1-C_6)alkyl-C(=O)-NR^5R^6, -(C_1-C_6)alkyl-OC(=O)-R^5, -(C_0-C_6)alkyl-C(=O)-OR^5, -O-(C_1-C_6)alkyl-C(=O)-OR^5, -NR^5-(C_1-C_6)alkyl-C(=O)-OR^6, -(C_0-C_6)alkyl-C(=O)-R^5, -O-(C_1-C_6)alkyl-C(=O)-R^5 and -NR^5-(C_1-C_6)alkyl-C(=O)-R^6;

R^5, R^6 and R^7 are each independently hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)alkylcyano, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl;

Any two radicals of R (R^5, R^6, or R^7) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

M^1 is selected from an optionally substituted aryl and heteroaryl;

M^3 is an optionally substituted radical selected from the group of -(C_3-C_7)cycloalkyl, aryl, heteroaryl, heterocycle, -(C_1-C_6)alkyl-R^{11}, -(C_1-C_6)alkylhalo, -(C_2-C_6)alkyl-$NR^{11}R^{12}$, -(C_2-C_6)alkyl-OR^{11} and -(C_2-C_6)alkyl-SR^{11}; and

R^{11} and R^{12} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl.

6. A compound according to claim 2 having the Formula (II), wherein:

X^2 is a nitrogen, an oxygen, or a sulfur atom, X^3 is a carbon atom or a nitrogen atom, X^4 is a carbon or a nitrogen atom, representing a 5 membered heteroaryl, which may further be substituted by 1 to 2 radicals A^m;

m is an integer ranging from 1 to 2;

A^m radicals are each independently selected from the group of hydrogen, halogen, -CN, -CF_3, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylcyano, -(C_1-C_6)alkylheteroaryl, -(C_1-C_6)alkylaryl, aryl, heteroaryl, heterocycle, -(C_0-C_6)alkyl-OR^1, -O-(C_2-C_6)alkyl-OR^1, -NR^1(C_2-C_6)alkyl-OR^2, -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -O-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -NR^1-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo-OR^1, -(C_1-C_6)alkylhalo-NR^1R^2, -NR^1-(C_2-C_6)alkyl-SR^2, -(C_0-C_6)alkyl-S(=O)-R^1, -NR^1-(C_1-C_6)alkyl-S(=O)-R^2, -(C_0-C_6)alkyl-$S(=O)_2$-R^1, -NR^1-(C_1-C_6)alkyl-$S(=O)_2$-R^2, -(C_0-C_6)alkyl-NR^1R^2, -NR^1-(C_2-C_6)alkyl-NR^2R^3, -(C_0-C_6)alkyl-$S(=O)_2NR^1R^2$, -NR^1-(C_1-C_6)alkyl-$S(=O)_2NR^2R^3$, -(C_0-C_6)alkyl-NR^1-$S(=O)_2R^2$, -NR^1-(C_2-C_6)alkyl-NR^2-$S(=O)_2R^3$, -(C_0-C_6)alkyl-C(=O)-NR^1R^2, -NR^1-(C_1-C_6)alkyl-C(=O)-NR^2R^3, -(C_0-C_6)alkyl-NR^1C(=O)-R^2, -NR^1-(C_2-C_6)alkyl-NR^2C(=O)-R^3, -NR^1-(C_2-C_6)alkyl-OC(=O)-R^2, -(C_0-C_6)alkyl-C(=O)-OR^1, -NR^1-(C_1-C_6)alkyl-C(=O)-OR^2, -(C_0-C_6)alkyl-C(=O)-R^1, -NR^1-(C_1-

C_6)alkyl-C(=O)-R^2, -(C_0-C_6)alkyl-NR^1-C(=O)-OR^2, -(C_0-C_6)alkyl-NR^1-C(=O)-NR^2R^3, and -NR^1-(C_2-C_6)alkyl-NR^2-C(=O)-NR^3R^4;

Any two radicals of A^m (A^1 and A^2) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

R^1, R^2, R^3 and R^4 are each independently hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)alkylcyano, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl;

Any two radicals of R (R^1, R^2, R^3 or R^4) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

n is an integer ranging from 1 to 2;

B^n radicals are each independently selected from the group of hydrogen, halogen, -CN, -CF_3, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylcyano, -(C_1-C_6)alkylheteroaryl, -(C_1-C_6)alkylaryl, aryl, heteroaryl, heterocycle, -(C_0-C_6)alkyl-OR^5, -O-(C_2-C_6)alkyl-OR^5, -NR^5(C_2-C_6)alkyl-OR^6, -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -O-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -NR^5-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo-OR^5, -(C_1-C_6)alkylhalo-NR^5R^6, -(C_0-C_6)alkyl-S-R^5, -O-(C_2-C_6)alkyl-S-R^5, -NR^5-(C_2-C_6)alkyl-S-R^6, -(C_0-C_6)alkyl-S(=O)-R^5, -O-(C_1-C_6)alkyl-S(=O)-R^5, -NR^5-(C_1-C_6)alkyl-S(=O)-R^6, -(C_0-C_6)alkyl-$S(=O)_2$-R^5, -O-(C_1-C_6)alkyl-$S(=O)_2$-R^5, -NR^5-(C_1-C_6)alkyl-$S(=O)_2$-R^6, -(C_0-C_6)alkyl-NR^5R^6, -O-(C_2-C_6)alkyl-NR^5R^6, -NR^5-(C_2-C_6)alkyl-NR^6R^7, -(C_0-C_6)alkyl-$S(=O)_2NR^5R^6$, -O-(C_1-C_6)alkyl-$S(=O)_2NR^5R^6$, -NR^5-(C_1-C_6)alkyl-$S(=O)_2NR^6R^7$, -(C_0-C_6)alkyl-NR^5-$S(=O)_2R^6$, -O-(C_2-C_6)alkyl-NR^5-$S(=O)_2R^6$, -NR^5-(C_2-C_6)alkyl-NR^6-$S(=O)_2R^7$, -(C_0-C_6)alkyl-C(=O)-NR^5R^6, -O-(C_1-C_6)alkyl-C(=O)-NR^5R^6, -NR^5-(C_1-C_6)alkyl-C(=O)-NR^6R^7, -(C_0-C_6)alkyl-NR^5C(=O)-R^6, -O-(C_2-C_6)alkyl-NR^5C(=O)-R^6, -NR^5-(C_2-C_6)alkyl-NR^6C(=O)-R^7, -O-(C_2-C_6)alkyl-OC(=O)-R^5, -NR^5-(C_2-C_6)alkyl-OC(=O)-R^6, -(C_0-C_6)alkyl-C(=O)-OR^5, -O-(C_1-C_6)alkyl-C(=O)-OR^5, -NR^5-(C_1-C_6)alkyl-C(=O)-OR^6, -(C_0-C_6)alkyl-C(=O)-R^5, -O-(C_1-

C_6)alkyl-C(=O)-R^5, -NR^5-(C_1-C_6)alkyl-C(=O)-R^6, -(C_0-C_6)alkyl-NR^5-C(=O)-OR^6, -(C_0-C_6)alkyl-NR^5-C(=O)-NR^6R^7, -O-(C_2-C_6)alkyl-NR^5-C(=O)-NR^6R^7 and -NR^5-(C_2-C_6)alkyl-NR^6-C(=O)-NR^7R^8;

R^5, R^6, R^7 and R^8 each independently hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl and heterocycle;

Any two radicals of of R (R^5, R^6, R^7 or R^8) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

M^1 is selected from an optionally substituted aryl and heteroaryl;

M^2 is a hydrogen or an optionally substituted -(C_1-C_6)alkyl-R^9;

R^9 is a hydrogen;

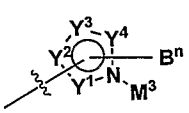
M^3 is an optionally substituted radical selected from the group of -(C_3-C_7)cycloalkyl, aryl, heteroaryl, heterocycle, -(C_1-C_6)alkyl-R^{11}, -(C_1-C_6)alkylhalo, -(C_2-C_6)alkyl-$NR^{11}R^{12}$, -(C_2-C_6)alkyl-OR^{11} and -(C_2-C_6)alkyl-SR^{11}; and

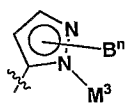
R^{11} and R^{12} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_1-C_6)alkylcyano, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl;

provided that according to proviso (i):

when M^3 is -(C_0)-R^{11} (that is when M^3 is -R^{11}), then R^{11} is not H;

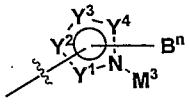
and provided that according to proviso (ii):



can not be


;

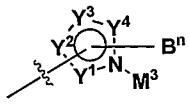
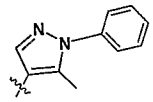
and provided that according to proviso (iii):

when M^1 is aryl, X^2 is C, X^3 is C, X^4 is N, then  is not linked to X^2;

and provided that according to proviso (iv):

A^1 and A^2 radicals are not linked to form an imidazopyridazinyl ring;

and provided that according to proviso (v):

when  is  and linked to X^4, X^2 is S, X^3 is C, X^4 is C, n is 1, A^1 is H, then M^1 can not be an optionally substituted aryl, 1-methyl-1H-indazol-4-yl, 1H-indazol-3-yl and 1H-indazol-4-yl;

and provided that according to proviso (vi):

when M^3 is 4-methylphenyl, then B^n can not be a phenyl;

and provided that according to proviso (vii):

when X^2 is S, X^3 is C, X^4 is C, n is 1, then A^1 when linked to either X^3 or X^4 is not pyridyl;

and provided that according to proviso (viii):

when X^2 is S, X^3 is C, X^4 is C, to provide a thiazole ring, n is 1, then A^1 is not an optionally substituted imidazolyl or triazolyl ring.

7. A compound according to claim 3 having the Formula (III), wherein:

m is an integer ranging from 1 to 2;

A^m radicals are each independently selected from the group of hydrogen, halogen, -CN, $-CF_3$, and an optionally substituted radical selected from the group of $-(C_1-C_6)$alkyl, $-(C_1-C_6)$alkylhalo, $-(C_3-C_7)$cycloalkyl, $-(C_1-C_6)$alkylcyano, heterocycle, $-(C_0-C_6)$alkyl-OR^1, $-(C_3-C_7)$cycloalkyl-(C_1-C_6)alkyl, $-NR^1-(C_3-C_7)$cycloalkyl-(C_1-C_6)alkyl, $-(C_1-C_6)$alkylhalo-OR^1, $-(C_1-C_6)$alkylhalo-NR^1R^2,

$(C_0\text{-}C_6)$alkyl-NR^1R^2, -NR^1-$(C_2\text{-}C_6)$alkyl-NR^2R^3, -$(C_0\text{-}C_6)$alkyl-C(=O)-NR^1R^2, -NR^1-$(C_1\text{-}C_6)$alkyl-C(=O)-NR^2R^3, -$(C_0\text{-}C_6)$alkyl-NR^1C(=O)-R^2, -NR^1-$(C_2\text{-}C_6)$alkyl-NR^2C(=O)-R^3, -$(C_0\text{-}C_6)$alkyl-C(=O)-R^1, and -NR^1-$(C_1\text{-}C_6)$alkyl-C(=O)-R^2;

R^1, R^2 and R^3 are each independently hydrogen or an optionally substituted radical selected from the group of -$(C_1\text{-}C_6)$alkylhalo, -$(C_1\text{-}C_6)$alkyl, -$(C_3\text{-}C_7)$cycloalkyl, -$(C_4\text{-}C_{10})$alkylcycloalkyl and heterocycle,

Any two radicals of R (R^1, R^2 or R^3) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

n is an integer ranging from 1 to 2;

B^n radicals are each independently selected from the group of hydrogen, halogen, -CN, -CF_3, and an optionally substituted radical selected from the group of -$(C_1\text{-}C_6)$alkyl, -$(C_1\text{-}C_6)$alkylhalo, -$(C_3\text{-}C_7)$cycloalkyl, -$(C_1\text{-}C_6)$alkylcyano, -$(C_1\text{-}C_6)$alkylheteroaryl, -$(C_1\text{-}C_6)$alkylaryl, aryl, heteroaryl, heterocycle, -$(C_0\text{-}C_6)$alkyl-OR^5, -O-$(C_2\text{-}C_6)$alkyl-OR^5, -$NR^5(C_2\text{-}C_6)$alkyl-OR^6, -$(C_3\text{-}C_7)$cycloalkyl-$(C_1\text{-}C_6)$alkyl, -O-$(C_3\text{-}C_7)$cycloalkyl-$(C_1\text{-}C_6)$alkyl, -NR^5-$(C_3\text{-}C_7)$cycloalkyl-$(C_1\text{-}C_6)$alkyl, -$(C_1\text{-}C_6)$alkylhalo-OR^5, -$(C_1\text{-}C_6)$alkylhalo-NR^5R^6, -$(C_0\text{-}C_6)$alkyl-S-R^5, -O-$(C_2\text{-}C_6)$alkyl-S-R^5, -NR^5-$(C_2\text{-}C_6)$alkyl-S-R^6, -$(C_0\text{-}C_6)$alkyl-S(=O)-R^5, -O-$(C_1\text{-}C_6)$alkyl-S(=O)-R^5, -NR^5-$(C_1\text{-}C_6)$alkyl-S(=O)-R^6, -$(C_0\text{-}C_6)$alkyl-$S(=O)_2$-R^5, -O-$(C_1\text{-}C_6)$alkyl-$S(=O)_2$-R^5, -NR^5-$(C_1\text{-}C_6)$alkyl-$S(=O)_2$-R^6, -$(C_0\text{-}C_6)$alkyl-NR^5R^6, -O-$(C_2\text{-}C_6)$alkyl-NR^5R^6, -NR^5-$(C_2\text{-}C_6)$alkyl-NR^6R^7, -$(C_0\text{-}C_6)$alkyl-$S(=O)_2NR^5R^6$, -O-$(C_1\text{-}C_6)$alkyl-$S(=O)_2NR^5R^6$, -NR^5-$(C_1\text{-}C_6)$alkyl-$S(=O)_2NR^6R^7$, -$(C_0\text{-}C_6)$alkyl-NR^5-$S(=O)_2R^6$, -O-$(C_2\text{-}C_6)$alkyl-NR^5-$S(=O)_2R^6$, -NR^5-$(C_2\text{-}C_6)$alkyl-NR^6-$S(=O)_2R^7$, -$(C_0\text{-}C_6)$alkyl-C(=O)-NR^5R^6, -O-$(C_1\text{-}C_6)$alkyl-C(=O)-NR^5R^6, -NR^5-$(C_1\text{-}C_6)$alkyl-C(=O)-NR^6R^7, -$(C_0\text{-}C_6)$alkyl-NR^5C(=O)-R^6, -O-$(C_2\text{-}C_6)$alkyl-NR^5C(=O)-R^6, -NR^5-$(C_2\text{-}C_6)$alkyl-NR^6C(=O)-R^7, -O-$(C_2\text{-}C_6)$alkyl-OC(=O)-R^5, -NR^5-$(C_2\text{-}C_6)$alkyl-OC(=O)-R^6, -$(C_0\text{-}C_6)$alkyl-C(=O)-OR^5, -O-$(C_1\text{-}C_6)$alkyl-C(=O)-OR^5, -NR^5-$(C_1\text{-}C_6)$alkyl-C(=O)-OR^6, -$(C_0\text{-}C_6)$alkyl-C(=O)-R^5, -O-$(C_1\text{-}C_6)$alkyl-C(=O)-R^5, -NR^5-$(C_1\text{-}C_6)$alkyl-C(=O)-R^6, -$(C_0\text{-}C_6)$alkyl-NR^5-C(=O)-

OR^6, $-(C_0-C_6)alkyl-NR^5-C(=O)-NR^6R^7$, $-O-(C_2-C_6)alkyl-NR^5-C(=O)-NR^6R^7$ and $-NR^5-(C_2-C_6)alkyl-NR^6-C(=O)-NR^7R^8$;

R^5, R^6, R^7 and R^8 each independently hydrogen or an optionally substituted radical selected from the group of $-(C_1-C_6)$alkylhalo, $-(C_1-C_6)$alkyl, $-(C_3-C_7)$cycloalkyl, $-(C_4-C_{10})$alkylcycloalkyl and heterocycle;

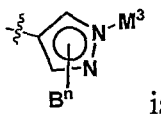
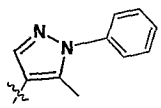
Any two radicals of of R (R^5, R^6, R^7 or R^8) may be taken together to form an optionally substituted 3 to 10 membered carbocyclic or heterocyclic ring;

M^1 is selected from an optionally substituted aryl and heteroaryl;

M^3 is an optionally substituted radical selected from the group of $-(C_3-C_7)$cycloalkyl, aryl, heteroaryl, heterocycle, $-(C_1-C_6)alkyl-R^{11}$, $-(C_1-C_6)$alkylhalo, $-(C_2-C_6)alkyl-NR^{11}R^{12}$, $-(C_2-C_6)alkyl-OR^{11}$ and $-(C_2-C_6)alkyl-SR^{11}$;

R^{11} and R^{12} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of $-(C_1-C_6)$alkylhalo, $-(C_1-C_6)$alkyl, $-(C_1-C_6)$alkylcyano, $-(C_3-C_7)$cycloalkyl, $-(C_4-C_{10})$alkylcycloalkyl, heteroaryl, $-(C_1-C_6)$alkylheteroaryl, aryl, heterocycle and $-(C_1-C_6)$alkylaryl;

provided that according to proviso (v):

when  is  , X^3 is C, n is 1, A^1 is H, then M^1 can not be an optionally substituted aryl, 1-methyl-1H-indazol-4-yl, 1H-indazol-3-yl and 1H-indazol-4-yl;

and provided that according to proviso (vi):

when M^3 is 4-methylphenyl, then B^n can not be a phenyl;

and provided that according to proviso (vii):

A^1 is not a pyridyl;

and provided that according to proviso (viii):

when X^3 is C to provide a thiazole ring, n is 1, then A^1 is not an optionally substituted imidazolyl or triazolyl ring.

8. A compound according to claim 4 having the Formula (IIIA), wherein:

A^1 radical is selected from the group of hydrogen, halogen, $-CF_3$, and an optionally substituted radical selected from the group of $-(C_1-C_6)$alkyl, $-(C_1-C_6)$alkylhalo, $-(C_3-C_7)$cycloalkyl and heterocycle;

n is an integer ranging from 1 to 2, and either;

(a) n is 1 and B^1 radical is selected from the group of hydrogen, halogen, $-CF_3$, and an optionally substituted radical selected from the group of $-(C_1-C_6)$alkyl, $-(C_1-C_6)$alkylhalo, $-(C_3-C_7)$cycloalkyl, $-(C_0-C_6)$alkyl-OR^5, and $-(C_3-C_7)$cycloalkyl-(C_1-C_6)alkyl; or

(b) n is 2, and B^1 and B^2 radicals are each independently selected from the group of $-CF_3$ and an optionally substituted radical selected from the group of $-(C_1-C_6)$alkyl, $-(C_1-C_6)$alkylhalo, $-(C_3-C_7)$cycloalkyl, and $-(C_3-C_7)$cycloalkyl-(C_1-C_6)alkyl;

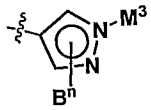
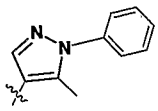
R^5 is selected from the group of hydrogen or an optionally substituted radical selected from the group of $-(C_1-C_6)$alkylhalo, $-(C_1-C_6)$alkyl, $-(C_3-C_7)$cycloalkyl, $-(C_4-C_{10})$alkylcycloalkyl and heterocycle;

M^1 is an optionally substituted aryl;

M^3 is an optionally substituted radical selected from the group of $-(C_3-C_7)$cycloalkyl, aryl, heteroaryl, heterocycle, $-(C_1-C_6)$alkyl-R^{11}, $-(C_1-C_6)$alkylhalo, $-(C_2-C_6)$alkyl-$NR^{11}R^{12}$, $-(C_2-C_6)$alkyl-OR^{11} and $-(C_2-C_6)$alkyl-SR^{11};

R^{11} and R^{12} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of $-(C_1-C_6)$alkylhalo, $-(C_1-C_6)$alkyl, $-(C_3-C_7)$cycloalkyl, $-(C_4-C_{10})$alkylcycloalkyl, heteroaryl, $-(C_1-C_6)$alkylheteroaryl, aryl, heterocycle and $-(C_1-C_6)$alkylaryl;

provided that according to proviso (v):

when  is  , X^3 is C, n is 1, A^1 is H, then M^1 can not be 1-methyl-1H-indazol-4-yl, 1H-indazol-3-yl and 1H-indazol-4-yl;

and provided that according to proviso (vii):

A^1 is not a pyridyl;

and provided that according to proviso (viii):

when X^3 is C, X^4 is C, to provide a thiazole ring, n is 1, then A^1 is not an optionally substituted imidazolyl or triazolyl ring.

9. A compound according to claim 4 having the Formula (IIIA), wherein:

A^1 radical is selected from the group of hydrogen, halogen, $-CF_3$, and an optionally substituted radical selected from the group of $-(C_1-C_6)$alkyl, $-(C_1-C_6)$alkylhalo, $-(C_3-C_7)$cycloalkyl and heterocycle;

n is an integer ranging from 1 to 2, and either;

(a) n is 1 and B^1 radical is selected from the group of hydrogen, halogen, $-CF_3$, and an optionally substituted radical selected from the group of $-(C_1-C_6)$alkyl, $-(C_1-C_6)$alkylhalo, $-(C_3-C_7)$cycloalkyl, $-(C_0-C_6)$alkyl-OR^5, and $-(C_3-C_7)$cycloalkyl-(C_1-C_6)alkyl; or

(b) n is 2, and B^1 and B^2 radicals are each independently selected from the group of $-CF_3$ and an optionally substituted radical selected from the group of $-(C_1-C_6)$alkyl, $-(C_1-C_6)$alkylhalo, $-(C_3-C_7)$cycloalkyl, and $-(C_3-C_7)$cycloalkyl-(C_1-C_6)alkyl;

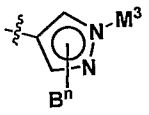
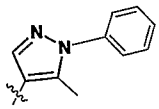
R^5 is selected from the group of hydrogen or an optionally substituted radical selected from the group of $-(C_1-C_6)$alkylhalo, $-(C_1-C_6)$alkyl, $-(C_3-C_7)$cycloalkyl, $-(C_4-C_{10})$alkylcycloalkyl and heterocycle;

M^1 is an optionally substituted heteroaryl;

M^3 is an optionally substituted radical selected from the group of -(C_3-C_7)cycloalkyl, aryl, heteroaryl, heterocycle, -(C_1-C_6)alkyl-R^{11}, -(C_1-C_6)alkylhalo, -(C_2-C_6)alkyl-$NR^{11}R^{12}$, -(C_2-C_6)alkyl-OR^{11} and -(C_2-C_6)alkyl-SR^{11};

R^{11} and R^{12} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl;

provided that according to proviso (v):

when  is  , X^3 is C, n is 1, A^1 is H, then M^1 can not be 1-methyl-1H-indazol-4-yl, 1H-indazol-3-yl and 1H-indazol-4-yl;

and provided that according to proviso (vii):

A^1 is not a pyridyl;

and provided that according to proviso (viii):

when X^3 is C, X^4 is C, to provide a thiazole ring, n is 1, then A^1 is not an optionally substituted imidazolyl or triazolyl ring.

10. A compound according to claim 4 having the Formula (IIIA), wherein:

A^1 radical is hydrogen,

n is an integer ranging from 1 to 2, and either;

(a) n is 1 and B^1 radical is selected from the group of hydrogen, -CF_3, -(C_1-C_6)alkyl and -(C_1-C_6)alkylhalo; or

(b) n is 2, and B^1 and B^2 radicals are each independently selected from the group of -CF_3 and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl and -(C_1-C_6)alkylhalo;

M^1 is an optionally substituted pyridyl;

M^3 is an optionally substituted radical selected from the group of -(C_3-C_7)cycloalkyl, aryl, heteroaryl, heterocycle, -(C_1-C_6)alkyl-R^{11}, -(C_1-C_6)alkylhalo, -(C_2-C_6)alkyl-$NR^{11}R^{12}$, -(C_2-C_6)alkyl-OR^{11} and -(C_2-C_6)alkyl-SR^{11}; and

R^{11} and R^{12} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl.

11. A compound according to claim 5 having the Formula (IIIB), wherein:

n is an integer ranging from 1 to 2, and either;

(a) n is 1 and B^1 radical is selected from the group of hydrogen, halogen, $-CF_3$, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_3-C_7)cycloalkyl, -(C_0-C_6)alkyl-OR^5, aryl, heteroaryl, and -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl; or

(b) n is 2, and B^1 and B^2 radicals are each independently selected from the group of $-CF_3$ and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_3-C_7)cycloalkyl, and -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl;

R^5 is selected from the group of hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl and heterocycle;

M^1 is an optionally substituted aryl;

M^3 is an optionally substituted radical selected from the group of -(C_3-C_7)cycloalkyl, aryl, heteroaryl, heterocycle, -(C_1-C_6)alkyl-R^{11}, -(C_1-C_6)alkylhalo, -(C_2-C_6)alkyl-$NR^{11}R^{12}$, -(C_2-C_6)alkyl-OR^{11} and -(C_2-C_6)alkyl-SR^{11}; and

R^{11} and R^{12} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl.

12. A compound according to claim 5 having the Formula (IIIB), wherein:n

n is an integer ranging from 1 to 2, and either;

(a) n is 1 and B^1 radical is selected from the group of hydrogen, halogen, -CF_3, and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_3-C_7)cycloalkyl, -(C_0-C_6)alkyl-OR^5, aryl, heteroaryl, and -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl; or

(b) n is 2, and B^1 and B^2 radicals are each independently selected from the group of -CF_3 and an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)alkylhalo, -(C_3-C_7)cycloalkyl, and -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl;

R^5 is selected from the group of hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl and heterocycle;

M^1 is an optionally substituted heteroaryl;

M^3 is an optionally substituted radical selected from the group of -(C_3-C_7)cycloalkyl, aryl, heteroaryl, heterocycle, -(C_1-C_6)alkyl-R^{11}, -(C_1-C_6)alkylhalo, -(C_2-C_6)alkyl-$NR^{11}R^{12}$, -(C_2-C_6)alkyl-OR^{11} and -(C_2-C_6)alkyl-SR^{11}; and

R^{11} and R^{12} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkylhalo, -(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_4-C_{10})alkylcycloalkyl, heteroaryl, -(C_1-C_6)alkylheteroaryl, aryl, heterocycle and -(C_1-C_6)alkylaryl.

13. A compound according to claim 5 having the Formula (IIIB), wherein:

n is an integer ranging from 1 to 2, and either;

(a) n is 1, and B^1 radical is selected from the group of hydrogen, $-CF_3$, $-(C_1-C_6)$alkyl and $-(C_1-C_6)$alkylhalo; or

(b) n is 2, and B^1 and B^2 radicals are each independently selected from the group of $-CF_3$ and an optionally substituted radical selected from the group of $-(C_1-C_6)$alkyl and $-(C_1-C_6)$alkylhalo;

M^1 is an optionally substituted pyridyl;

M^3 is an optionally substituted radical selected from the group of $-(C_3-C_7)$cycloalkyl, aryl, heteroaryl, heterocycle, $-(C_1-C_6)$alkyl-R^{11}, $-(C_1-C_6)$alkylhalo, $-(C_2-C_6)$alkyl-$NR^{11}R^{12}$, $-(C_2-C_6)$alkyl-OR^{11} and $-(C_2-C_6)$alkyl-SR^{11}; and

R^{11} and R^{12} are selected from the group of a hydrogen or an optionally substituted radical selected from the group of $-(C_1-C_6)$alkylhalo, $-(C_1-C_6)$alkyl, $-(C_3-C_7)$cycloalkyl, $-(C_4-C_{10})$alkylcycloalkyl, heteroaryl, $-(C_1-C_6)$alkylheteroaryl, aryl, heterocycle and $-(C_1-C_6)$alkylaryl.

14. A compound according to claims 1 to 13, which can exist as optical isomers, wherein said compound is either the racemic mixture or one or both of the individual optical isomers.

15. A compound according to claims 1 to 2, wherein said compound is selected from:

3-(1,3-Dimethyl-1*H*-pyrazol-4-yl)-*N*-methyl-*N*-phenyl-1,2,4-thiadiazol-5-amine

3-(1,5-Dimethyl-1*H*-pyrazol-4-yl)-*N*-methyl-*N*-phenyl-1,2,4-thiadiazol-5-amine

and a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof.

16. A compound according to claims 1 to 3, wherein said compound is selected from:

N-(2-Fluorophenyl)-3-(1-(4-methoxybenzyl)-3-methyl-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

N-(2-Fluorophenyl)-3-(1-(4-methoxybenzyl)-5-methyl-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

3-(1-(4-Methoxybenzyl)-3-methyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-(4-Methoxybenzyl)-5-methyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-(4-Methoxybenzyl)-1*H*-pyrazol-4-yl)-*N*-phenyl-1,2,4-thiadiazol-5-amine

4-(1-(4-Methoxybenzyl)-3-methyl-1H-pyrazol-4-yl)-N-phenylthiazol-2-amine

4-(1-(4-Methoxybenzyl)-5-methyl-1H-pyrazol-4-yl)-N-phenylthiazol-2-amine

3-(5-Methyl-1-phenyl-1*H*-pyrazol-4-yl)-*N*-phenyl-1,2,4-thiadiazol-5-amine

3-(3-Methyl-1-propyl-1*H*-pyrazol-4-yl)-*N*-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine

4-(1-Benzyl-1H-pyrazol-4-yl)-N-phenylthiazol-2-amine

4-(1-Isopropyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)thiazol-2-amine

4-(1-Ethyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)thiazol-2-amine

4-(1-Methyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)thiazol-2-amine

and a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof.

17. A compound according to claim 4, wherein said compound is selected from:

4-(1-Propyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)thiazol-2-amine

N-(Benzo[d][1,3]dioxol-5-yl)-4-(1-propyl-1H-pyrazol-4-yl)thiazol-2-amine

N-(2-Fluorophenyl)-4-(1-propyl-1H-pyrazol-4-yl)thiazol-2-amine

4-(3-Methyl-1-propyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)thiazol-2-amine

4-(3-Methyl-1-propyl-1H-pyrazol-4-yl)-N-(6-methylpyridin-2-yl)thiazol-2-amine

N-(5-Chloropyridin-2-yl)-4-(3-methyl-1-propyl-1H-pyrazol-4-yl)thiazol-2-amine

N-(6-Methoxypyridin-3-yl)-4-(3-methyl-1-propyl-1H-pyrazol-4-yl)thiazol-2-amine
N-(2-Methoxypyridin-3-yl)-4-(3-methyl-1-propyl-1H-pyrazol-4-yl)thiazol-2-amine
4-(1-Propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)thiazol-2-amine
4-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)thiazol-2-amine
N-(Pyridin-2-yl)-4-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)thiazol-2-amine

and a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof.

18. A compound according to claim 5, wherein said compound is selected from:

3-(1-Ethyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine
3-(1-Ethyl-1H-pyrazol-4-yl)-N-(6-methoxypyridin-2-yl)-1,2,4-thiadiazol-5-amine
3-(1-Ethyl-1H-pyrazol-4-yl)-N-(6-morpholinopyridin-2-yl)-1,2,4-thiadiazol-5-amine
3-(1-Ethyl-3-methyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine
3-(1-Propyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine
3-(1-(3-Fluorobenzyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine
3-(1-(3-Fluorobenzyl)-1H-pyrazol-4-yl)-N-phenyl-1,2,4-thiadiazol-5-amine
N-(Pyridin-2-yl)-3-(1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine
3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(pyridine-2-yl)-1,2,4-thiadiazol-5-amine
3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine hydrochloride
3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(6-methylpyridin-2-yl)-1,2,4-

thiadiazol-5-amine

3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(6-ethylpyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(6-fluoropyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(5-fluoropyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(6-methoxypyridin-2-yl)-1,2,4-thiadiazol-5-amine

N-(6-Cyclobutoxypyridin-2-yl)-3-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(6-morpholinopyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(5-morpholinopyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(6-(trifluoromethyl)pyridin-2-yl)-1,2,4-thiadiazol-5-amine

N-(5-Chloropyridin-2-yl)-3-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

6-(3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-ylamino)nicotinonitrile

3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-N-(pyrazin-2-yl)-1,2,4-thiadiazol-5-amine

6-(3-(1-(Cyclopropylmethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-ylamino)nicotinamide

3-(1-(Cyclobutylmethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-(2-Morpholinoethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine

N-(Pyridin-2-yl)-3-(1-((tetrahydrofuran-2-yl)methyl)-1H-pyrazol-4-yl)-1,2,4-

thiadiazol-5-amine

N-(Pyridin-2-yl)-3-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

3-(1-(2-Methoxyethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine

2-(4-(5-(Pyridin-2-ylamino)-1,2,4-thiadiazol-3-yl)-1H-pyrazol-1-yl)ethanol

3-(1-Cyclobutyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-(3-Fluoro-4-methoxyphenyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-(4-Fluorophenyl)-5-methyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-(4-Fluorophenyl)-5-methyl-1H-pyrazol-4-yl)-N-phenyl-1,2,4-thiadiazol-5-amine

3-(1-Propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine

N-(6-Methylpyridin-2-yl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

N-(6-Methoxypyridin-3-yl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

N-(2-Methoxypyridin-3-yl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

N-(5-Chloropyridin-2-yl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

3-(1-Propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)-1,2,4-thiadiazol-5-amine

N-(3,5-Difluoropyridin-2-yl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

3-(1-Propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-N-(quinolin-2-yl)-1,2,4-thiadiazol-5-amine

N-(2-Methylpyridin-4-yl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-

1,2,4-thiadiazol-5-amine

N-(2-Fluorophenyl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

N-(2,5-Difluorophenyl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

N-(Benzo[d][1,3]dioxol-5-yl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

N-(4-Morpholinophenyl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

N-(3-Methoxyphenyl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

3-(1-Propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-N-(3-(trifluoromethyl)phenyl)-1,2,4-thiadiazol-5-amine

N-(4-Chlorophenyl)-3-(1-propyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

3-(1-(Cyclopropylmethyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine

N-(Pyridin-2-yl)-3-(1-(2,2,2-trifluoroethyl)-3-(trifluoromethyl)-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

3-(3,5-Dimethyl-1-propyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-(Cyclopropylmethyl)-3,5-dimethyl-1H-pyrazol-4-yl)-N-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(1-(Cyclopropylmethyl)-3,5-dimethyl-1H-pyrazol-4-yl)-N-(6-methylpyridin-2-yl)-1,2,4-thiadiazol-5-amine

3-(3-Methyl-1-propyl-1H-pyrazol-4-yl)-N-(6-methylpyridin-2-yl)-1,2,4-thiadiazol-5-amine

N-(6-Ethylpyridin-2-yl)-3-(3-methyl-1-propyl-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine

3-(3-Methyl-1-propyl-1H-pyrazol-4-yl)-N-(6-(trifluoromethyl)pyridin-2-yl)-

1,2,4-thiadiazol-5-amine
3-(3-Methyl-1-propyl-1H-pyrazol-4-yl)-N-(3-(trifluoromethyl)pyridin-2-yl)-1,2,4-thiadiazol-5-amine
N-(5-Chloropyridin-2-yl)-3-(3-methyl-1-propyl-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine
N-(5-Fluoropyridin-2-yl)-3-(3-methyl-1-propyl-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine
6-(3-(3-Methyl-1-propyl-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-ylamino)nicotinonitrile
3-(3-Methyl-1-propyl-1H-pyrazol-4-yl)-N-(6-morpholinopyridin-2-yl)-1,2,4-thiadiazol-5-amine
N-(6-Methoxypyridin-2-yl)-3-(3-methyl-1-propyl-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine
N-(6-Fluoropyridin-2-yl)-3-(3-methyl-1-propyl-1H-pyrazol-4-yl)-1,2,4-thiadiazol-5-amine
3-(3-methyl-1-propyl-1H-pyrazol-4-yl)-N-(pyridin-3-yl)-1,2,4-thiadiazol-5-amine

and a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof.

19. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claims 1 to 18 and a pharmaceutically acceptable carrier and/or excipient.

20. A method of treating or preventing a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the effect of A_3 antagonists, comprising administering to a mammal in need of such treatment or prevention, an effective amount of a compound/composition according to claims 1 to 19.

21. A method useful for treating or preventing ocular disorders such as ocular hypertension, glaucoma, normal tension glaucoma, neurodegenerative disease conditions of the retina and the optic nerve, retinal dystrophies, age-related Macular degeneration, and conditions of the eye such as conjunctivitis, keratoconjunctivitis sicca, and vernal conjunctivitis, comprising administering to a mammalian patient in need of such treatment an effective amount of a compound/composition according to claims 1 to 19.

22. A method useful for treating or preventing inflammatory or obstructive airway diseases, airway inflammation-related bronchial hyperractivity, asthma of whatever type, including non-allergic and allergic asthma (mild to severe), bronchitic asthma, exercice-induced asthma, occupational asthma and asthma induced following bacterial infection, morning dipping, comprising administering to a mammalian patient in need of such treatment an effective amount of a compound/composition according to claims 1 to 19.

23. A method useful for treating or preventing bronchitis of whatever type; aluminosis, antracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis, comprising administering to a mammalian patient in need of such treatment an effective amount of a compound/composition according to claims 1 to 19.

24. A method useful for treating or preventing eosinophil related disorders such as hypereosinophilia with eosinophil infiltration in the airways, eosinophilic oesophagitis, parasitic eosinophilia, inflammatory or allergic conditions of the skin, for example psoriasis, contact dermatitis, alopecia areata, erythema multiforma, scleroderma, atopic dermatis, urticaria, lupus erythematosus or epidermolysis bullosa acquisita, comprising administering to a mammalian

patient in need of such treatment an effective amount of a compound/composition according to claims 1 to 19.

25. A method useful for synergistically enhancing the chemotherapeutic treatment of tumors expressing adenosine A_3 receptors comprising administering to a mammal in need thereof an effective amount of a high affinity adenosine A_3 receptor antagonists either prior to, during or subsequent to administration of a chemotherapeutic cancer agent, comprising administering to a mammalian patient in need of such treatment an effective amount of a compound/composition according to claims 1 to 19.

26. A method useful for treating or preventing central nervous system disorders selected from the group consisting of anxiety disorders: Agoraphobia, Generalized Anxiety Disorder (GAD), Obsessive-Compulsive Disorder (OCD), Panic Disorder, Posttraumatic Stress Disorder (PTSD), Social Phobia, Other Phobias, Substance-Induced Anxiety Disorder, comprising administering to a mammalian patient in need of such treatment an effective amount of a compound/composition according to claims 1 to 19.

27. A method useful for treating or preventing central nervous system disorders selected from the group consisting of mood disorders: Bipolar Disorders (I & II), Cyclothymic Disorder, Depression, Dysthymic Disorder, Major Depressive Disorder, Substance-Induced Mood Disorder, comprising administering to a mammalian patient in need of such treatment an effective amount of a compound/composition according to claims 1 to 19.

28. A method useful for treating or preventing central nervous system disorders selected from the group consisting of eating disorders including anorexia nervosa, bulimia, comprising administering to a mammalian patient in need of such

treatment an effective amount of a compound/composition according to claims 1 to 19.

29. A method useful for treating or preventing disorders including personality disorders such a borderline personality disorders; autism; ADHD; Tourette's syndrome; sexual disorders; migraine; diabetic neuropathy; obesity; addiction; sleep disorders; arthritis; chronic fatigue syndrome and irritable bowel syndrome, comprising administering to a mammalian patient in need of such treatment an effective amount of a compound/composition according to claims 1 to 19.

30. A method useful for treating or preventing inflammation and/or neurodegeneration, resulting from traumatic brain injury, stroke, hemorrhagic stroke, ischemia, spinal cord injury, cerebral hypoxia, cerebral haemorrhage or intracranial hematoma, comprising administering to a mammalian patient in need of such treatment an effective amount of a compound/composition according to claims 1 to 19.

31. A method useful for treating or preventing sensory, motor or cognitive symptoms resulting from traumatic brain injury, stroke, hemorrhagic stroke, ischemia, spinal cord injury, cerebral hypoxia, cerebral haemorrhage or intracranial haematoma, comprising administering to a mammalian patient in need of such treatment an effective amount of a compound/composition according to claims 1 to 19.

32. A method useful for treating or preventing ischemic cardiac diseases, including myocardial infarction, ischemic heart disease and related disease, comprising administering to a mammalian patient in need of such treatment an effective amount of a compound/composition according to claims 1 to 19.

33. A method useful for treating or preventing renal failure and consequences due to ischemia, comprising administering to a mammalian patient in need of such

treatment an effective amount of a compound/composition according to claims 1 to 19.

34. A method useful for treating or preventing hepatic failure and consequences due to ischemia, comprising administering to a mammalian patient in need of such treatment an effective amount of a compound/composition according to claims 1 to 19.

35. Use of a compound according to claims 1 to 18 to prepare a tracer for imaging an adenosine A_3 receptor.

36. Use of a compound according to claims 1 to 18 in the manufacture of a medicament for a treatment or prevention as defined in any of claims 20 to 34.