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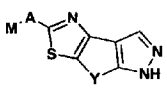
(54) Title: NOVEL TETRAHYDROPYRAZOLO[3,4-B]AZEPINE DERIVATIVES AND THEIR USE AS ALLOSTERIC MODULATORS OF METABOTROPIC GLUTAMATE RECEPTORS

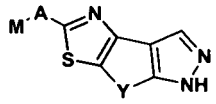


(I)

(57) Abstract: The present invention relates to novel compounds of Formula (I), wherein M, A and Y are defined as in Formula (I); invention compounds are modulators of metabotropic glutamate receptors - subtype 4 ("$mGluR_4$") which are useful for the treatment or prevention of central nervous system disorders as well as other disorders modulated by $mGluR_4$ 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 $mGluR_4$ is involved.

NOVEL TETRAHYDROPYRAZOLO[3,4-*b*]AZEPINE DERIVATIVES AND THEIR USE AS ALLOSTERIC MODULATORS OF METABOTROPIC GLUTAMATE RECEPTORS

SUMMARY OF THE INVENTION



(I)

The present invention relates to novel compounds of Formula (I), wherein M, A and Y are defined as in Formula (I); invention compounds are modulators of metabotropic glutamate receptors – subtype 4 ("mGluR$_4$") which are useful for the treatment or prevention of central nervous system disorders as well as other disorders modulated by mGluR$_4$ 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 mGluR$_4$ is involved.

BACKGROUND OF THE INVENTION

Glutamate is the major amino-acid transmitter in the mammalian central nervous system (CNS). Glutamate plays a major role in numerous physiological functions, such as learning and memory but also sensory perception, development of synaptic plasticity, motor control, respiration and regulation of cardiovascular function. Furthermore, glutamate is at the center of several different neurological and psychiatric diseases, where there is an imbalance in glutamatergic neurotransmission.

Glutamate mediates synaptic neurotransmission through the activation of ionotropic glutamate receptor channels (iGluRs), namely the NMDA, AMPA and kainate receptors which are responsible for fast excitatory transmission (Nakanishi et al., (1998) Brain Res. Rev., 26:230-235).

In addition, glutamate activates metabotropic glutamate receptors (mGluRs) which have a more modulatory role that contributes to the fine-tuning of synaptic efficacy.

The mGluRs are G protein-coupled receptors (GPCRs) with seven-transmembrane spanning domains and belong to GPCR family 3 along with the calcium-sensing, GABAb and pheromone receptors.

The mGluR family is composed of eight members. They are classified into three groups (group I comprising $mGluR_1$ and $mGluR_5$; group II comprising $mGluR_2$ and $mGluR_3$; group III comprising $mGluR_4$, $mGluR_6$, $mGluR_7$ and $mGluR_8$) according to sequence homology, pharmacological profile and nature of intracellular signalling cascades activated (Schoepp et al., (1999) Neuropharmacology, 38:1431-1476).

Glutamate activates the mGluRs through binding to the large extracellular amino-terminal domain of the receptor, herein called the orthosteric binding site. This activation induces a conformational change of the receptor which results in the activation of the G-protein and intracellular signalling pathways.

In the central nervous system, $mGluR_4$ receptors are expressed most intensely in the cerebellar cortex, basal ganglia, sensory relay nuclei of the thalamus and hippocampus (Bradley et al., (1999) Journal of Comparative Neurology, 407:33-46; Corti et al., (2002) Neuroscience, 110:403-420). The $mGluR_4$ subtype is negatively coupled to adenylate cyclase via activation of the Gαi/o protein, is expressed primarily on presynaptic terminals, functioning as an autoreceptor or heteroceptor and activation of $mGluR_4$ leads to decreases in transmitter release from presynaptic terminals (Corti et al., (2002) Neuroscience, 110:403-420; Millan et al., (2002) Journal of Biological

Chemistry, 277:47796-47803; Valenti et al., (2003) Journal of Neuroscience, 23:7218-7226).

Orthosteric agonists of $mGluR_4$ are not selective and activate the other Group III mGluRs (Schoepp et al., (1999) Neuropharmacology, 38:1431-1476). The Group III orthosteric agonist L-AP4 (L-2-amino-4-phosphonobutyrate) was able to reduce motor deficits in animal models of Parkinson's disease (Valenti et al., (2003) J. Neurosci., 23:7218-7226) and decrease excitotoxicity (Bruno et al., (2000) J. Neurosci., 20;6413-6420) and these effects appear to be mediated through $mGluR_4$ (Marino et al., (2005) Curr. Topics Med. Chem., 5:885-895). In addition to L-AP4, ACPT-1, another selective group III mGluR agonist has been shown to caused a dose and structure-dependent decrease in haloperidol-induced catalepsy and attenuated haloperidol-increased Proenkephalin mRNA expression in the striatum (Konieczny et al., (2007) Neuroscience, 145:611-620). Furthemore, Lopez et al. (2007, J. Neuroscience, 27:6701-6711) have shown that bilateral infusions of ACPT-I or L-AP4 into the globus pallidus fully reversed the severe akinetic deficits produced by 6-hydroxydopamine lesions of nigrostriatal dopamine neurons in a reaction-time task without affecting the performance of controls. In addition, the reversal of haloperidol-induced catalepsy by intrapallidal ACPT-1 was prevented by concomitant administration of a selective group III receptor antagonist (*RS*)-alpha-cyclopropyl-4-phosphonophenylglycine. The opposite effects produced by group III mGluR activation in the SNr strongly suggest a role of $mGluR_4$ rather than others mGluR receptor sub-types in normalizing basal ganglia activity (Lopez et al. 2007).

These results suggest that, among mGluR subtypes, $mGluR_4$ is believed to be the most interesting novel drug target for the treatment of Parkinson's disease (for a review see Conn et al., (2005) Nature Review Neuroscience, 6:787-798).

Symptoms of Parkinson's disease appear to be due to an imbalance in the direct and indirect output pathways of the basal ganglia, and reduction of transmission at the

inhibitory GABAergic striato-pallidal synapse in the indirect pathway may result in alleviation of these symptoms (Marino et al., (2002) Amino Acids, 23:185-191).

$mGluR_4$ is more abundant in striato-pallidal synapses than in striato-nigral synapses, and its localization suggests function as a presynaptic heteroreceptor on GABAergic neurons (Bradley et al., (1999) Journal of Comparative Neurology, 407:33-46) suggesting that selective activation or positive modulation of $mGluR_4$ would decrease GABA release in this synapse thereby decreasing output of the indirect pathway and reducing or eliminating the Parkinson's disease symptoms. Classical treatment of Parkinsonism typically involves the use of levodopa combined with carbidopa (SINEMET™) or benserazide (MADOPAR™). Dopamine agonists such as bromocriptine (PARLODEL™), lisuride and pergolide (CELANCE™) act directly on dopamine receptors and are also used for the treatment of Parkinsonism. These molecules have the same side-effect profile as levodopa.

A new avenue for developing selective compounds acting at mGluRs is to identify molecules that act through allosteric mechanisms, modulating the receptor by binding to a site different from the highly conserved orthosteric binding site.

Positive allosteric modulators of mGluRs have emerged recently as novel pharmacological entities offering this attractive alternative. This type of molecule has been discovered for $mGluR_1$, $mGluR_2$, $mGluR_4$, $mGluR_5$, $mGluR_7$ and $mGluR_8$ (Knoflach F. et al. (2001) Proc. Natl. Acad. Sci. USA, 98:13402-13407; Johnson M.P. et al., (2002) Neuropharmacology, 43:799-808; O'Brien J.A. et al., (2003) Mol. Pharmacol., 64:731-740; Johnson M.P. et al., (2003) J. Med. Chem., 46:3189-3192; Marino M.J. et al., (2003) Proc. Natl. Acad. Sci. USA, 100:13668-13673; Mitsukawa K. et al., (2005) Proc. Natl. Acad. Sci. USA, 102(51):18712-18717; Wilson J. et al., (2005) Neuropharmacology, 49:278; for a review see Mutel V., (2002) Expert Opin. Ther. Patents, 12:1-8; Kew J.N., (2004) Pharmacol. Ther., 104(3):233-244; Johnson M.P. et al., (2004) Biochem. Soc. Trans., 32:881-887; recently Ritzen A., Mathiesen, J.M. and Thomsen C., (2005) Basic Clin. Pharmacol. Toxicol., 97:202-213).

In particular molecules have been described as $mGluR_4$ positive allosteric modulators (Maj et al., (2003) Neuropharmacology, 45:895-906; Mathiesen et al., (2003) British Journal of Pharmacology, 138:1026-1030). It has been demonstrated that such molecules have been characterized in *in vitro* systems as well as in rat brain slices where they potentiated the effect of L-AP4 in inhibiting transmission at the striatopallidal synapse. These compounds do not activate the receptor by themselves (Marino et al., (2003) Proc. Nat. Acad. Sci. USA, 100:13668-13673). Rather, they enable the receptor to produce a maximal response to a concentration of glutamate or the Group III orthosteric agonist L-AP4 which by itself induces a minimal response.

PHCCC (*N*-phenyl-7-(hydroxyimino)cyclopropa[*b*]chromen-l*a*-carboxamide), a positive allosteric modulator of $mGluR_4$ not active on other mGluRs (Maj et al., (2003) Neuropharmacology, 45:895-906), has been shown to be efficacious in animal models of Parkinson's disease thus representing a potential novel therapeutic approach for Parkinson's disease as well as for other motor disorders and disturbances (Marino et al., (2003) Proc. Nat. Acad. Sci. USA, 100:13668-13673), neurodegeneration in Parkinson's disease (Marino et al., (2005) Curr. Topics Med. Chem., 5:885-895; Valenti et al., (2005) J. Pharmacol. Exp. Ther., 313:1296-1304; Vernon et al., (2005) Eur. J. Neurosci., 22:1799-1806, Battaglia et al., (2006) J. Neurosci., 26:7222-7229), and neurodegeneration in Alzheimer's disease or due to ischemic or traumatic insult (Maj et al., (2003) Neuropharmacology, 45:895-906).

PHCCC also has been shown to be active in an animal model of anxiety (Stachowicz et al., (2004) Eur. J. Pharmacol., 498:153-156). Previously, ACPT-1 has been shown to produce a dose-dependent anti-conflict effect after intrahippocampal administration and anti-depressant-like effects in rats after intracerebroventricular administration (Tatarczynska et al., (2002) Pol. J. Pharmacol., 54(6):707-710). More recently, ACPT-1 has also been shown to have anxiolytic-like effects in the stress-induced hyperthermia, in the elevated-plus maze in mice and in the Vogel conflict test in rats when injected intraperitoneally (Stachowicz et al., (2009) Neuropharmacology, 57(3): 227-234).

Activation of $mGluR_4$ receptors which are expressed in α– and F-cells in the islets of Langerhans inhibits glucagon secretion. Molecules which activate or potentiate the agonist activity of these receptors may be an effective treatment for hyperglycemia, one of the symptoms of type 2 diabetes (Uehara et al., (2004) Diabetes, 53:998-1006).

The β-chemokine RANTES is importantly involved in neuronal inflammation and has been implicated in the pathophysiology of multiple sclerosis. Activation of Group III mGluRs with L-AP4 reduced the synthesis and release of RANTES in wild-type cultured astrocytes, whereas the ability of L-AP4 to inhibit RANTES was greatly decreased in astrocyte cultures from $mGluR_4$ knockout mice (Besong et al., (2002) Journal of Neuroscience, 22:5403-5411). These data suggest that positive allosteric modulators of $mGluR_4$ may be an effective treatment for neuroinflammatory disorders of the central nervous system, including multiple sclerosis and related disorders.

Two different variants of the $mGluR_4$ receptor are expressed in taste tissues and may function as receptors for the umami taste sensation (Monastyrskaia et al., (1999) Br. J Pharmacol., 128:1027-1034; Toyono et al., (2002) Arch. Histol. Cytol., 65:91-96). Thus positive allosteric modulators of $mGluR_4$ may be useful as taste agents, flavour agents, flavour enhancing agents or food additives.

There is anatomical evidence that the majority of vagal afferents innervating gastric muscle express group III mGluRs ($mGluR_4$, $mGluR_6$, $mGluR_7$ and $mGluR_8$) and actively transport receptors to their peripheral endings (Page et al., (2005) Gastroenterology, 128:402-10). Recently, it was shown that the activation of peripheral group III mGluRs inhibited vagal afferents mechanosensitivity in vitro which translates into reduced triggering of transient lower esophageal sphincter relaxations and gastroesophageal reflux in vivo (Young et al., (2008) Neuropharmacol, 54:965-975). Labelling for $mGluR_4$ and $mGluR_8$ was abundant in gastric vagal afferents in the. nodose ganglion, at their termination sites in the nucleus tractus solitarius and in gastric vagal motoneurons. These data suggest that positive allosteric modulators of $mGluR_4$

may be an effective treatment for gastroesophageal reflux disease (GERD) and lower esophageal disorders and gastro-intestinal disorders.

International patent publication WO2005/007096 has described $mGluR_4$ receptor positive allosteric modulator useful, alone or in combination with a neuroleptic agent, for treating or preventing movement disorders. However, none of the specifically disclosed compounds are structurally related to the compounds of the invention.

Recently, new $mGluR_4$ receptor positive allosteric modulators have been described: pyrazolo[3,4-*d*]pyrimidine derivatives (Niswender et al., (2008) Bioorganic & Medicinal Chemistry Letters, 18(20):5626-5630), functionalized benzylidene hydrazinyl-3-methylquinazoline and *bis*-2,3-dihydroquinazolin-4(1*H*)-one (Williams et al., (2009) Bioorganic & Medicinal Chemistry Letters, 19:962-966) and heterobiarylamides (Engers et al, (2009) Journal of Medicinal Chemistry, 52 (14), 4115-4118). Niswender et al., described (±)-*cis*-2-(3,5-dichlorophenylcarbamoyl)cyclohexane carboxylic acid (2008) Molecular Pharmacology, 74(5):1345-1358), as a positive allosteric modulator of $mGluR_4$ also having agonist activity. This moderately active molecule has demonstrated evidence of efficacy following icv injection in rat models of Parkinson's disease. International patent publications WO2009/010454 and WO2009/010455 have mentioned amido derivatives and novel heteroaromatic derivatives, respectively, as positive allosteric modulators of metabotropic glutamate receptors. The subject of the latter case has been examined in the following article East Stephen P. et al., (2010) Expert Opin. Ther. Patents, 20 (3) 441-445. Finally, Williams R. et al., described in (2010) ACS Chemical Neuroscience, 1(6): 411-419, the "Re-exploration of the PHCCC scaffold".

International patent publication WO2010/079238 has described novel tricyclic heteroaromatic derivatives and their use as positive allosteric modulators of mGluRs. More recently, a review on recent progress on the identification of metabotropic glutamate 4 receptor ligands and their potential utility as CNS therapeutics (Robichaud A. et al., (14th June 2011) ACS Chemical Neuroscience, DOI: 10.1021/cn200043e, http://pubs.acs.org) has cited some of the examples described in the WO2010/079238

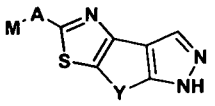
patent application; Hong S.-P et al, (20th June 2011) J. Med. Chem., DOI: 10.1021/jm200290z, http://pubs.acs.org) have described tricyclic thiazolopyrazole derivatives as metabotropic glutamate receptor 4 positive allosteric modulators.

The present inventors have discovered novel thiazole compounds of general Formula (I) which, surprisingly, show potent activity and selectivity on the $mGluR_4$ receptor. The compounds of the invention demonstrate advantageous properties over compounds of the prior art. Improvements have been observed in one or more of the following characteristics of the compounds of the invention: the potency on the target, the selectivity for the target, the bioavailability, the brain penetration, and the activity in behavioural models.

Such aminothiazole derivatives are useful for 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 $mGluR_4$ modulators. In the case of the treatment of movement disorders such as Parkinson's disease, the compounds of the invention can be used alone or in combination with an agent selected from the group consisting of: levodopa, levodopa with a selective extracerebral decarboxylase inhibitor, carbidopa, entacapone, a COMT inhibitor, a dopamine agonist, an anticholinergic, a cholinergic agonist, a butyrophenone neuroleptic agent, a diphenylbutylpiperidine neuroleptic agent, a heterocyclic dibenzazepine neuroleptic agent, an indolone neuroleptic agent, a phenothiazine neuroleptic agent, a thioxanthene neuroleptic agent, an NMDA receptor antagonist, an MAO-B inhibitor, an $mGluR_5$ antagonist or an A_{2A} antagonist.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to compounds having metabotropic glutamate receptor 4 modulator 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:

M is an optionally subsituted heteroaryl;

A is NH or O;

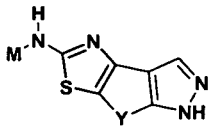
Y is selected from the group of -CO-CR^1R^2-NR^5- and -CR^1R^2-CR^3R^4-NR^5-;

R^1, R^2, R^3 and R^4 are each independently selected from the group of hydrogen, halogen, -CN, -CF_3 or an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)haloalkyl, -(C_3-C_7)cycloalkyl, aryl, heteroaryl, heterocycle, -(C_1-C_6)alkylene-aryl, -(C_1-C_6)alkylene-heteroaryl, -(C_1-C_6)alkylene-heterocycle, -O-(C_0-C_6)alkyl, -N-((C_0-C_6)alkyl)$_2$, -(C_1-C_6)alkyl-O-(C_0-C_6)alkyl, and -(C_1-C_6)alkyl-N-((C_0-C_6)alkyl)$_2$;

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

R^5 is selected from the group of hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)haloalkyl, -(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylene-(C_1-C_6)haloalkyl, -(C_1-C_6)alkylene-(C_3-C_7)halocycloalkyl, aryl, heteroaryl, heterocycle, -(C_1-C_6)alkylene-aryl, -(C_1-C_6)alkylene-heteroaryl, -(C_1-C_6)alkylene-heterocycle, -(C_2-C_6)alkyl-O-(C_0-C_6)alkyl, and -(C_2-C_6)alkyl-N-((C_0-C_6)alkyl)$_2$.

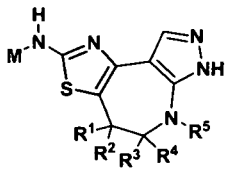
In a more preferred aspect of Formula (I), the invention provides a compound according to Formula (II):



(II)

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

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



(III)

R^1, R^2, R^3 or R^4 are each independently selected from the group of hydrogen, halogen, -CN, $-CF_3$ or an optionally substituted radical selected from the group of $-(C_1-C_6)$alkyl, $-(C_1-C_6)$haloalkyl, $-(C_3-C_7)$cycloalkyl, aryl, heteroaryl, heterocycle, $-(C_1-C_6)$alkylene-aryl, $-(C_1-C_6)$alkylene-heteroaryl, $-(C_1-C_6)$alkylene-heterocycle, $-O-(C_0-C_6)$alkyl, $-N-((C_0-C_6)alkyl)_2$, $-(C_1-C_6)$alkyl-O-(C_0-C_6)alkyl, and $-(C_1-C_6)$alkyl-N-$((C_0-C_6)alkyl)_2$;

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; and

R^5 is selected from the group of hydrogen or an optionally substituted radical selected from the group of $-(C_1-C_6)$alkyl, $-(C_1-C_6)$haloalkyl, $-(C_3-C_7)$cycloalkyl, $-(C_1-C_6)$alkylene-(C_1-C_6)haloalkyl, $-(C_1-C_6)$alkylene-(C_3-C_7)halocycloalkyl, aryl, heteroaryl, heterocycle, $-(C_1-C_6)$alkylene-aryl, $-(C_1-C_6)$alkylene-heteroaryl, $-(C_1-C_6)$alkylene-heterocycle, $-(C_1-C_6)$alkylene-(C_3-C_7)cycloalkyl, $-(C_2-C_6)$alkyl-O-(C_0-C_6)alkyl, and $-(C_2-C_6)$alkyl-N-$((C_0-C_6)alkyl)_2$.

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

R^1, R^2, R^3 or R^4 are each independently selected from the group of hydrogen, halogen, -CN, $-CF_3$ or an optionally substituted radical selected from the group of $-(C_1-C_6)$alkyl, $-(C_1-C_6)$haloalkyl, $-(C_3-C_7)$cycloalkyl, aryl, heteroaryl, heterocycle, $-(C_1-C_6)$alkylene-aryl, $-(C_1-C_6)$alkylene-heteroaryl, $-(C_1-C_6)$alkylene-heterocycle, $-O-(C_0-C_6)$alkyl, $-N-((C_0-C_6)alkyl)_2$, $-(C_1-C_6)$alkyl-O-(C_0-C_6)alkyl, and $-(C_1-C_6)$alkyl-N-$((C_0-C_6)alkyl)_2$;

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; and

R^5 is selected from the group of hydrogen or an optionally substituted radical selected from the group of $-(C_1-C_6)$alkyl, $-(C_1-C_6)$haloalkyl, $-(C_3-C_7)$cycloalkyl, $-(C_1-C_6)$alkylene-(C_1-C_6)haloalkyl, $-(C_1-C_6)$alkylene-(C_3-C_7)halocycloalkyl, aryl, heteroaryl, heterocycle, $-(C_1-C_6)$alkylene-aryl, $-(C_1-C_6)$alkylene-heteroaryl, $-(C_1-C_6)$alkylene-heterocycle, $-(C_2-C_6)$alkyl-O-(C_0-C_6)alkyl, and $-(C_2-C_6)$alkyl-N-$((C_0-C_6)alkyl)_2$.

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

M is an optionnally substituted pyridinyl, pyrimidinyl, thiadiazolyl, triazinyl, thiazolyl and oxadiazolyl;

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

R^5 is selected from the group of hydrogen or an optionally substituted radical selected from the group of methyl, ethyl, isopropyl, cyclobutyl, methyl-ethylene-O-methyl, tetrahydrofuranyl, methylene-amide, methylene-trifluoromethyl, methylene-cyclopropyl, methylene-cyclobutyl, methylene-cyclopentyl, methylene-cyclohexyl, methylene-phenyl, methylene-tetrahydrofuranyl, methylene-pyrazolyl, methylene-isoxazolyl, methylene-oxazolyl, methylene-triazolyl, methylene-thiazolyl, methylene-pyrrolyl, methylene-imidazolyl, methylene-pyridinyl, methylene-pyrimidinyl, methylene-piperidinyl, ethylene-OH, ethylene-O-methyl, ethylene-O-isopropyl, ethylene-methylamine, ethylene-sulfonyl-methyl, ethylene-trifluoromethyl, ethylene-phenyl, ethylene-pyridinyl, ethylene-cyclopropyl and propylene-O-methyl.

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

M is selected from the group of pyridinyl, pyrimidinyl, thiadiazolyl and triazinyl which can each be substituted by hydrogen, methyl, fluoro, chloro, methoxy, amino, hydroxyl, methylenehydroxy or fluoromethylene;

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

R^5 is selected from the group of hydrogen or an optionally substituted radical selected from the group of methyl, ethyl, isopropyl, cyclobutyl, methyl-ethylene-O-methyl, tetrahydrofuranyl, methylene-amide, methylene-trifluoromethyl, methylene-cyclopropyl, methylene-cyclobutyl, methylene-cyclopentyl, methylene-cyclohexyl, methylene-phenyl, methylene-tetrahydrofuranyl, methylene-pyrazolyl, methylene-isoxazolyl, methylene-oxazolyl, methylene-triazolyl, methylene-thiazolyl, methylene-pyrrolyl, methylene-imidazolyl, methylene-pyridinyl, methylene-pyrimidinyl, methylene-piperidinyl, ethylene-OH, ethylene-O-methyl, ethylene-O-isopropyl, ethylene-methylamine, ethylene-sulfonyl-methyl, ethylene-trifluoromethyl, ethylene-phenyl, ethylene-pyridinyl, ethylene-cyclopropyl and propylene-O-methyl.

Particular preferred compounds of the invention are compounds as mentioned in the following list (List of Particular Preferred Compounds), as well as a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof and an *N*-oxide form thereof:

6-Methyl-*N*-(4-methylpyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-methyl-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-Ethyl-*N*-(4-methylpyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-(Cyclopropylmethyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-Isopropyl-*N*-(4-methylpyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine

N-(5-Fluoropyrimidin-2-yl)-6-isopropyl-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-(2-Methoxyethyl)-*N*-(4-methylpyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-Methyl-*N*-(5-methyl-1,2,4-thiadiazol-3-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoro-4-methylpyrimidin-2-yl)-6-methyl-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(4-Methylpyrimidin-2-yl)-6-((tetrahydrofuran-2-yl)methyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-(1-Methoxypropan-2-yl)-*N*-(4-methylpyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(2-methoxyethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-(2-Methoxyethyl)-*N*-(6-methylpyridin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(6-Fluoropyridin-2-yl)-6-(2-methoxyethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyridin-2-yl)-6-(2-methoxyethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-((1-Methyl-1*H*-pyrazol-3-yl)methyl)-*N*-(4-methylpyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N,*N*-Dimethyl-2-(2-(4-methylpyrimidin-2-ylamino)-4,5-dihydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-6(8*H*)-yl)acetamide
6-(2-Methoxyethyl)-*N*-(4-methoxypyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-(2-Methoxyethyl)-*N*-(5-methyl-1,2,4-thiadiazol-3-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
2-(2-(5-Fluoropyrimidin-2-ylamino)-4,5-dihydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-6(8*H*)-yl)ethanol
N^2-(6-(2-Methoxyethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-yl)pyridine-2,6-diamine
N-(5-Fluoropyrimidin-2-yl)-6-((5-methylisoxazol-3-yl)methyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-((3,5-Dimethylisoxazol-4-yl)methyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-((2-isopropyloxazol-4-yl)methyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(pyridin-2-ylmethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(pyridin-4-ylmethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(2-(methylsulfonyl)ethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(3,3,3-trifluoropropyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine

N-(5-Fluoropyrimidin-2-yl)-6-(2,2,2-trifluoroethyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(tetrahydrofuran-3-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(2-(methylamino)ethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(3-methoxypropyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-Ethyl-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-((3-methylisoxazol-5-yl)methyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-(Cyclopentylmethyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-(Cyclopropylmethyl)-*N*-(4-methylpyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-(Cyclohexylmethyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-(Cyclopropylmethyl)-*N*-(6-methylpyridin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-(Cyclopropylmethyl)-*N*-(6-fluoropyridin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-((5-Chloropyridin-2-yl)methyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-((5-isopropylisoxazol-3-yl)methyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(2-isopropoxyethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-(Cyclobutylmethyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-Benzyl-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-((3-Methylisoxazol-5-yl)methyl)-*N*-(4-methylpyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-((tetrahydrofuran-2-yl)methyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(pyrimidin-2-ylmethyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
2-(6-(2-Methoxyethyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-ylamino)pyrimidin-5-ol
N-(5-Fluoropyrimidin-2-yl)-6-(((*R*)-tetrahydrofuran-2-yl)methyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-((2-methyl-2*H*-1,2,3-triazol-4-yl)methyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
(6-(6-(2-Methoxyethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-ylamino)pyridin-2-yl)methanol
6-(2-Methoxyethyl)-*N*-(2-methylpyrimidin-4-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine

6-(2-Methoxyethyl)-*N*-(pyrimidin-4-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-((1*H*-Pyrazol-5-yl)methyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo [3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-((4-Bromo-1*H*-pyrazol-5-yl)methyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,8-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-(4-Chlorobenzyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(2-methylbenzyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(3-methoxybenzyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine
6-((5-Fluoropyridin-2-yl)methyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,7-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-((5-(trifluoromethyl)pyridin-2-yl)methyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-((4-methylpyridin-2-yl)methyl)-4,5,6,7-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-((3-Chloropyridin-2-yl)methyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,7-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-phenethyl-4,5,6,7-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(3-Fluoro-6-methylpyridin-2-yl)-6-(2-methoxyethyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-(3-Chlorobenzyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine
4-((2-(5-Fluoropyrimidin-2-ylamino)-4,5-dihydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-6(7*H*)-yl)methyl)benzonitrile
N-(5-Fluoropyrimidin-2-yl)-6-(4-(trifluoromethyl)benzyl)-4,5,6,7-tetrahydropyrazolo [3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-((6-methylpyridin-2-yl)methyl)-4,5,6,7-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(2-(pyridin-2-yl)ethyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-((1-methyl-1*H*-1,2,4-triazol-5-yl)methyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-((1-methyl-1*H*-1,2,4-triazol-3-yl)methyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-(2-Chlorobenzyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine
6-(4-Fluorobenzyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine
6-((2-(5-Fluoropyrimidin-2-ylamino)-4,5-dihydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-6(7*H*)-yl)methyl)nicotinonitrile
N-(5-Fluoropyrimidin-2-yl)-6-((5-methoxypyridin-2-yl)methyl)-4,5,6,7-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(piperidin-4-ylmethyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine

6-((5-Chlorothiazol-2-yl)methyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,7-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-((1-methyl-1*H*-imidazol-4-yl)methyl)-4,5,6,7-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-(1-(5-Chloropyridin-2-yl)ethyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,7-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-Cyclobutyl-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*]thiazolo [4,5-*d*]azepin-2-amine
N-(6-(Fluoromethyl)pyridin-2-yl)-6-(2-methoxyethyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine and
N-(5-Fluoropyrimidin-2-yl)-6-(2-methoxyethyl)-4-methyl-4,5,6,7-tetrahydropyrazolo [3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine.

Particularly relevant to the present invention is the tautomeric pair that exists for the pyrazole ring, illustrated below:

In this specification, reference to a generic formula or a compound as such indicating one tautomer is to be understood to refer to the tautomeric pair and the other tautomer thereof.

The disclosed compounds also include all pharmaceutically acceptable isotopic variations, in which at least one atom is replaced by an atom having the same atomic number, but an atomic mass different from the atomic mass usually found in nature. Examples of isotopes suitable for inclusion in the disclosed compounds include, without limitation, isotopes of hydrogen, such as ^{2}H and ^{3}H; isotopes of carbon, such as ^{13}C and ^{14}C; isotopes of nitrogen, such as ^{15}N; isotopes of oxygen, such as ^{17}O and ^{18}O; isotopes of phosphorus, such as ^{32}P and ^{33}P; isotopes of sulfur, such as ^{35}S; isotopes of fluorine, such as ^{18}F; and isotopes of chlorine, such as ^{36}Cl. Use of isotopic variations (e.g., deuterium, ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements. Additionally, certain isotopic variations of the disclosed compounds may incorporate a radioactive isotope (e.g., tritium, ^{3}H, or ^{14}C), which may be useful in drug

and/or substrate tissue distribution studies. Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labelled compounds of Formula (I) to (III) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples using appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

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 the case where a subscript is the integer 0 (zero) and the radical to which the subscript refers is alkyl, this indicates the radical is a hydrogen atom.

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 "alkylene" includes both straight and branched difunctional saturated hydrocarbon radicals and may be methylene, ethylene, *n*-propylene, *i*-propylene, *n*-butylene, *i*-butylene, *s*-butylene, *t*-butylene, *n*-pentylene, *i*-pentylene, *t*-pentylene, *neo*-pentylene, *n*-hexylene, *i*-hexylene or *t*-hexylene.

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.

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 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, pyridinyl, thiazolyl, isothiazolyl, furyl, pyrrolyl, triazolyl, imidazolyl, triazinyl, oxadiazolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolonyl, oxazolonyl, thiazolonyl, tetrazolyl, thiadiazolyl, benzoimidazolyl, benzooxazolyl, benzothiazolyl, tetrahydrotriazolopyridinyl, tetrahydrotriazolopyrimidinyl, benzofuryl, benzothiophenyl, thionaphthyl, indolyl, isoindolyl, pyridonyl, pyridazinyl, pyrazinyl, pyrimidinyl, quinolyl, phtalazinyl, naphthyridinyl, quinoxalinyl, quinazolyl, imidazopyridinyl, oxazolopyridinyl, thiazolopyridinyl, imidazopyridazinyl, oxazolopyridazinyl, thiazolopyridazinyl, cynnolyl, pteridinyl, furazanyl, benzotriazolyl, pyrazolopyridinyl and purinyl.

In this specification, unless stated otherwise, the term "alkylene-aryl", "alkylene-heteroaryl" and "alkylene-cycloalkyl" 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)alkylene-aryl" 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)alkylene-heteroaryl" 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-pyridinylmethyl, 3-pyridinylmethyl, 4-pyridinylmethyl, 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.

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, pyridinyl, pyrimidinyl, 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, dihydropyrrolyl isoxazolyl, isothiazolyl, isoindolinonyl, dihydropyrrolo[1,2-*b*]pyrazolyl, oxazolyl, oxazolidinonyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, tetrahydropyridinyl, pyrimidinyl, 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 "haloalkyl" means an alkyl radical as defined above, substituted with one or more halo radicals. The term "(C_1-C_6)haloalkyl" may include, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl and difluoroethyl. The term "O-C_1-C_6-haloalkyl" may

include, but is not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy and fluoroethoxy.

In this specification, unless stated otherwise, the term "haloalkylene" means an alkylene radical as defined above, substituted with one or more halo radicals. The term "(C_1-C_6)haloalkylene" may include, but is not limited to, fluoromethylene, difluoromethylene, fluoroethylene and difluoroethylene. The term "O-C_1-C_6-haloalkylene" may include, but is not limited to, fluoromethylenoxy, difluoromethylenoxy and fluoroethylenoxy.

In this specification, unless stated otherwise, the term "cyanoalkyl" 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, (C_1-C_6)alkyl, hydroxy, (C_1-C_6)alkylene-oxy, mercapto, aryl, heterocycle, heteroaryl, (C_1-C_6)alkylene-aryl, (C_1-C_6)alkylene-heterocycle, (C_1-C_6)alkylene-heteroaryl, halogen, trifluoromethyl, pentafluoroethyl, cyano, cyanomethyl, nitro, amino, amido, amidinyl, carboxyl, carboxamide, (C_1-C_6)alkylene-oxycarbonyl, carbamate, sulfonamide, ester and sulfonyl.

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 "positive allosteric modulator of $mGluR_4$" or "allosteric modulator of $mGluR_4$" 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

Allosteric modulators of $mGluR_4$ 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 allosteric modulators of $mGluR_4$ 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 allosteric modulators of $mGluR_4$, 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 and the like, parenterally in the form of solutions for injection, topically in the form of onguents 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 allosteric modulators of $mGluR_4$ 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 allosteric modulators of $mGluR_4$ 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 for example, by subcutaneously implantation or by intramuscular injection. Thus, for example, as an emulsion in an acceptable oil, or ion exchange resins, or as sparingly soluble derivatives, for example, as sparingly soluble salts.

Preferably disclosed allosteric modulators of $mGluR_4$ 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 and intranasal.

Classical treatment of Parkinsonism typically involves the use of levodopa combined with carbidopa (SINEMET™) or benserazide (MADOPAR™). Dopamine agonists such as bromocriptine (PARLODEL™), lisuride and pergolide (CELANCE™) act direcly on dopamine receptors and are also used for the treatment of Parkinsonism.

METHODS OF SYNTHESIS

The compounds according to the invention, in particular the compounds according to the Formula (I) to (III), 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) to (III).

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).

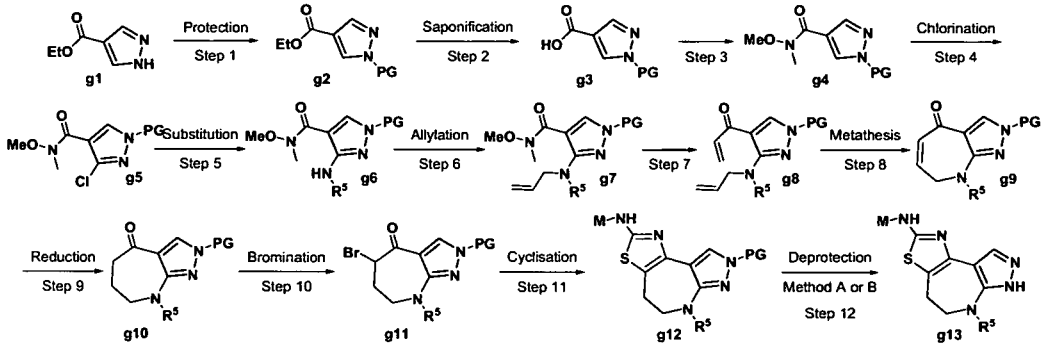
Many of the heterocyclic compounds of the invention can be prepared using synthetic routes well known in the art (Katrizky A.R. and. Rees C.W., (1984) *Comprehensive Heterocyclic Chemistry*, Pergamon Press).

The product from the reaction can be isolated and purified by 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.

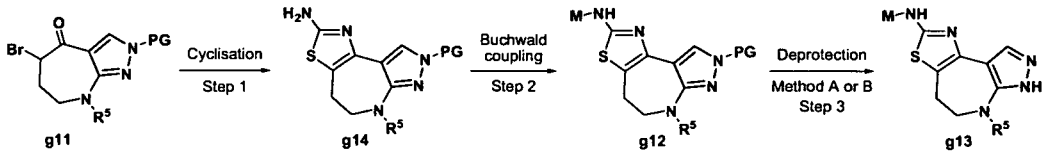
In one embodiment of the present invention, compounds of Formula (III) may be prepared according to the synthetic sequences illustrated in Scheme 1. Pyrazole **g1** can be protected by *p*-methoxybenzyl, for example, using standard conditions. Then compound **g2** may be hydrolyzed and the resulting carboxylic acid **g3** can be transformed into the corresponding Weinreb amide **g4**. Functionalized pyrazole **g5** can be obtained from deprotonation of pyrazole **g4** using LDA as a base in THF at -78°C followed by the addition of hexachloroethane. The subsequent chloropyrazole **g5** may

be substituted by primary amine to yield aminopyrazole **g6** which can then be reacted with allylbromide in the presence of NaH to give the tertiary amine **g7**. Vinyl Grignard reagent can be added on the Weinreb amide **g7** to generate the compound **g8** which can undergo metathesis using Grubbs catalysts. The resulting α,β-unsaturated ketone **g9** can be reduced in the presence of ammonium formate and $Pd(OH)_2$. Subsequently, ketone **g10** can be transformed into bromoketone **g11**, which in the presence of substituted thiourea can be cyclized into an aminothiazole **g12**. Finally, the expected compound **g13** can be obtained via deprotection in the presence of TFA or a mixture of TFA/TfOH at room temperature.



Scheme 1

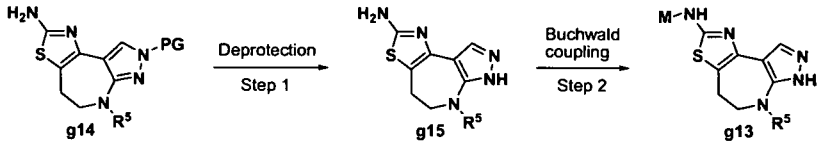
In one embodiment of the present invention, compounds of Formula (III) may be prepared according to the synthetic sequences illustrated in Scheme 2. Bromoketone **g11**, described above, can be submitted to cyclization in the presence of thiourea to yield aminothiazole **g14**. Primary amine **g14** can be coupled to heteroaryl halide M-X, using Buchwald conditions with $Pd(OAc)_2$ and Josiphos ligand, under microwave conditions, to yield compound **g12** which can be finally deprotected under acidic conditions as described above to give compound **g13**.



Scheme 2

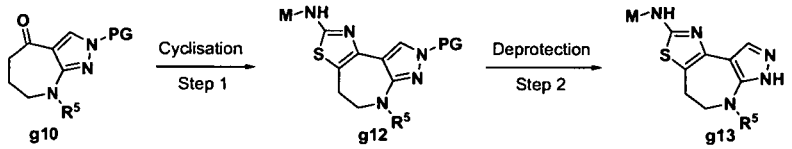
In one embodiment of the present invention, compounds of Formula (III) may be prepared according to the synthetic sequences illustrated in Scheme 3. Pyrazole **g14**

described above can be deprotected under acidic conditions and can be submitted to Buchwald coupling in the presence of heteroaryl halide M-X, $Pd_2(dba)_3$, Xantphos and in a solvent such as toluene to yield the final compound **g13**.



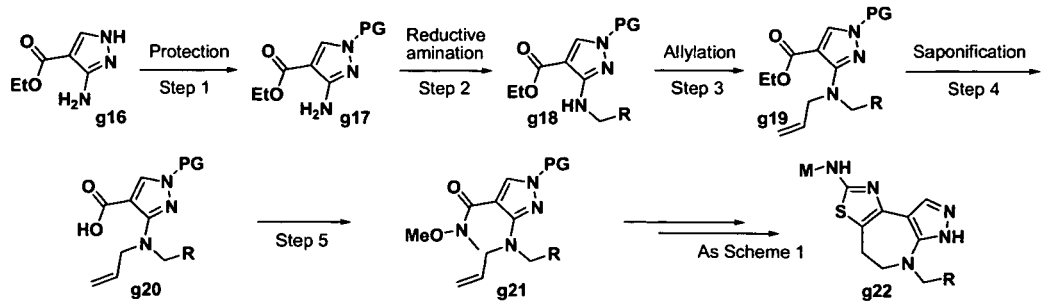
Scheme 3

In one embodiment of the present invention, compounds of Formula (III) may be prepared according to the synthetic sequences illustrated in Scheme 4. Ketone **g10** can be converted directly to the substituted aminothiazole **g12** in the presence of a thiourea, diiodine and in a solvent such as pyridine. After deprotection under acidic conditions, the desired compound **g13** can be obtained.



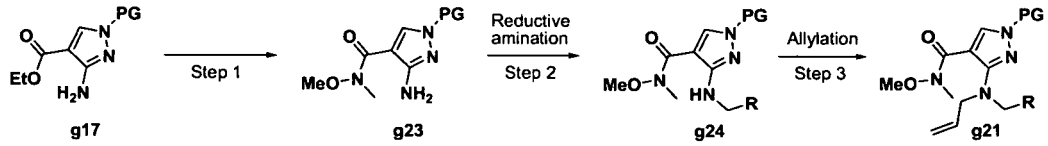
Scheme 4

In one embodiment of the present invention, compounds of Formula (III) may be prepared according to the synthetic sequences illustrated in Scheme 5. Pyrazole **g16** can be protected by *p*-methoxybenzyl, for example, using standard conditions. Then the primary amine **g17** can be converted into tertiary amine by being submitted first to a reductive amination followed by an allylation under standard conditions known from persons skilled in the art. After saponification of **g19**, the carboxylic acid can be transformed into the Weinreb amide **g21** which after six steps yielded the desired compound **g22** as described above in Scheme 1.



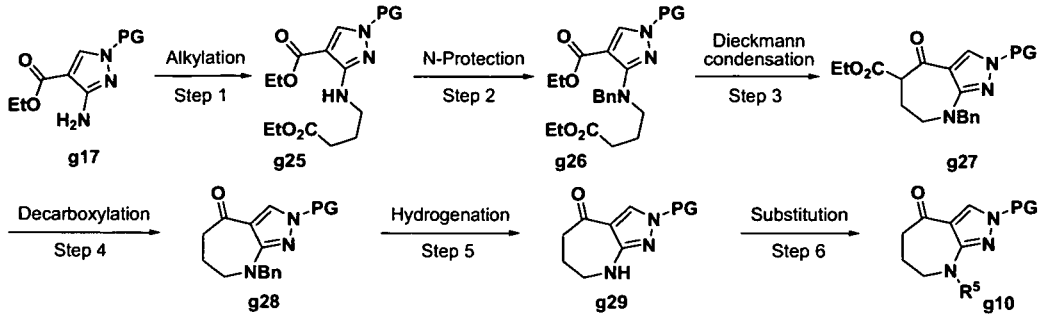
Scheme 5

In one embodiment of the present invention, compounds of Formula (III) may be prepared according to the synthetic sequences illustrated in Scheme 6. The ester **g17** can be directly transformed into the Weinreb amide **g23** in the presence of trimethylaluminum and *N,O*-dimethylhydroxylamine in a solvent such as DCM. After reductive amination followed by allylation, the tertiairy amine **g21** can be used as in Scheme 1 to yield the final compound **g13**.



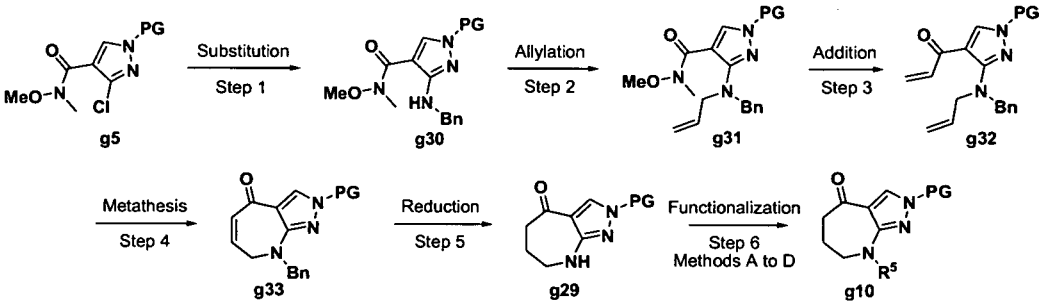
Scheme 6

In another embodiment of the invention, compounds of Formula (III) can be prepared as described in Scheme 7. Ethyl 5-amino-1-(4-methoxybenzyl)-1*H*-pyrazole-4-carboxylate **g17** can be alkylated with 4-bromobutyric acid ethyl ester at 150°C in NMP in the presence of K_2CO_3 to yield **g25**. In turn, this can be alkylated with benzyl bromide under similar conditions to yield **g26**. Dieckmann cyclization using LiHMDS, warming the reaction from 0°C to 70°C results in formation of the azepane ring **g27**. The pendent ethyl carboxylate group can then be hydrolyzed and decarboxylated by treatment with KOH in ethylene glycol, with heating at 110°C for 1 hour to furnish **g28**. The benzyl protecting group can then be removed by hydrogenation using $Pd(OH)_2$ in EtOH and AcOH at 50°C. Alkylation of the resulting free azepane **g29** with an alkyl halide at elevated temperature in the presence of a base such as K_2CO_3 results in formation of **g10**. In turn, **g10** can afford compounds of Formula (III), according to the synthetic route described in Scheme 1.



Scheme 7

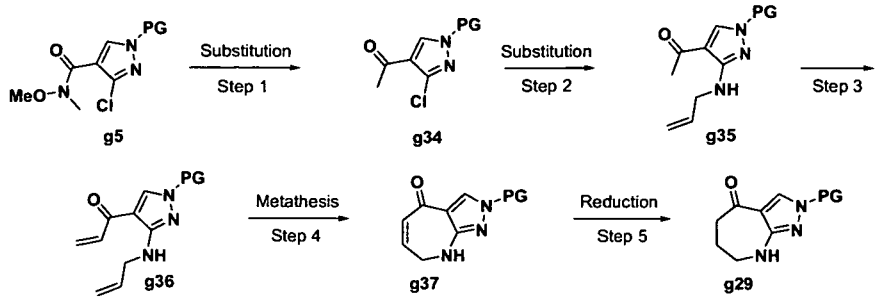
In one embodiment of the present invention, compounds of Formula (III) may be prepared according to the synthetic sequences illustrated in Scheme 8. Chloropyrazole **g5** may be substituted by phenylmethanamine to yield aminopyrazole **g30** which can then be reacted with allylbromide in the presence of NaH to give the tertiairy amine **g31**. Vinyl Grignard reagent can be added on the Weinreb amide **g31** to generate the compound **g32** which can undergo metathesis using Grubbs catalysts. The resulting α,β-unsaturated ketone **g33** can be reduced and also deprotected in the presence of ammonium formate and $Pd(OH)_2$. Subsequently, the amine **g29** can be functionalized by R^5X in the presence of different bases such as NaH, LiHMDS, KOtBu, and in a solvent such as THF to yield the compound **g10**. Compound **g10** can then undergo Steps 10 to 12 in Scheme 1 to give the expected aminothiazole **g13**.



Scheme 8

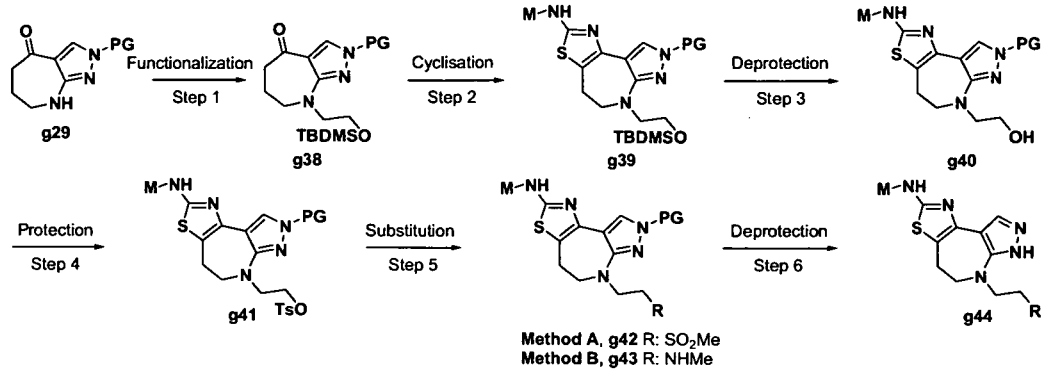
In one embodiment of the present invention, compounds of Formula (III) may be prepared according to the synthetic sequences illustrated in Scheme 9. Weinreb amide **g5** may be converted into ketone **g34** in the presence of methylmagnesium bromide. Then the chloropyrazole **g34** can be substituted by allylamine under microwave conditions followed by direct α-methylenation of the ketone moiety in the presence of

formaldehyde, diisopropylammonium-2,2,2-trifluoroacetate and a catalytic amount of acid such as TFA to give the α,β-unsaturated ketone **g36**. As described above **g36** can undergo metathesis using Grubbs catalysts, the resulting α,β-unsaturated ketone can be reduced to yield to compound **g29** which can lead to aminothiazole **g13** as in Scheme1.



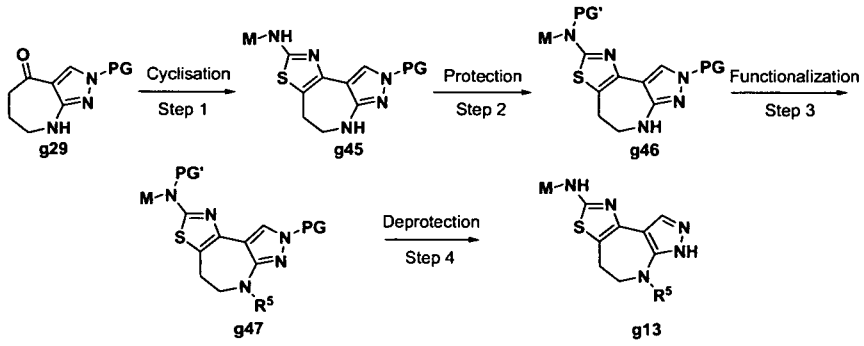
Scheme 9

In one embodiment of the present invention, compounds of Formula (III) may be prepared according to the synthetic sequences illustrated in Scheme 10. The secondary amine **g29** can be functionalized by ethoxy(*tert*-butyl)dimethylsilane in the presence of a base such as KO*t*Bu. The ketone **g38** in the presence of a thiourea and diiodine can lead to the aminothiazole **g39**. The TBDMS group can be gently removed in the presence of an acid such as HCl in a protic solvent such as methanol to yield the free hydroxyl function in the compound **g40**. Subsequently the hydroxyl function can be transformed into a good leaving group such as tosylate using standard conditions which can be displaced for example, by a sulfinate such as sodium methane sulfinate, an amine such as methanamine and the like to yield **g42** or **g43** respectively. After deprotection under acidic conditions, the expected compound **g44** is obtained.



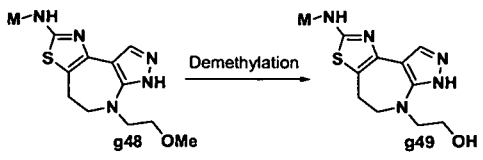
Scheme 10

In one embodiment of the present invention, compounds of Formula (III) may be prepared according to the synthetic sequences illustrated in Scheme 11. The ketone **g29** in the presence of a thiourea and diiodine can lead to the aminothiazole **g45**. The aminothiazole **g45** can be protected selectively by *p*-methoxybenzyl in the presence of a base such as NaH and in a solvent such as DMF. Then the secondary amine **g46** can be functionalized by methods described above and finally deprotected under acidic conditions to afford the desired compound **g13**.



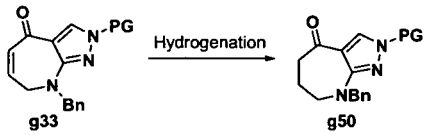
Scheme 11

In one embodiment of the present invention, compounds of Formula (III) may be prepared according to the synthetic sequences illustrated in Scheme 12. The ether **g48** can be demethylated in the presence of BBr_3 using standard methods well known from persons skilled in the art to yield the hydroxy compound **g49**.



Scheme 12

In one embodiment of the present invention, compounds of Formula (III) may be prepared according to the synthetic sequences illustrated in Scheme 13. **g50** as an intermediate in the general Scheme 1 can be synthesized from the selective reduction of the double bond in the presence of hydrogen and $Pd(OH)_2$ in a solvent such as a mixture of ethanol and acetic acid.

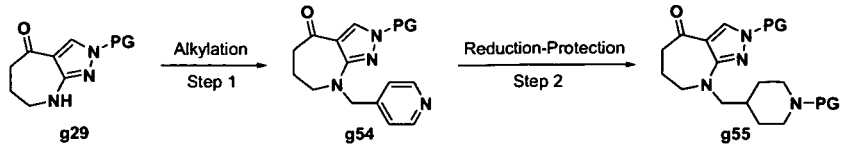


Scheme 13

In one embodiment of the present invention, compounds of Formula (III) may be prepared according to the synthetic sequences illustrated in Scheme 14. **g51** having a SEM group as protecting group can be submitted to functionalization as described above. The resulting ketone **g52** in the presence of trimethylphenylammonium tribromide in a solvent such as chloroform can be α-brominated with concomitant cleavage of the SEM. Finally the α-bromoketone **g53** can be transformed into aminothiazole **g13** using method described above.

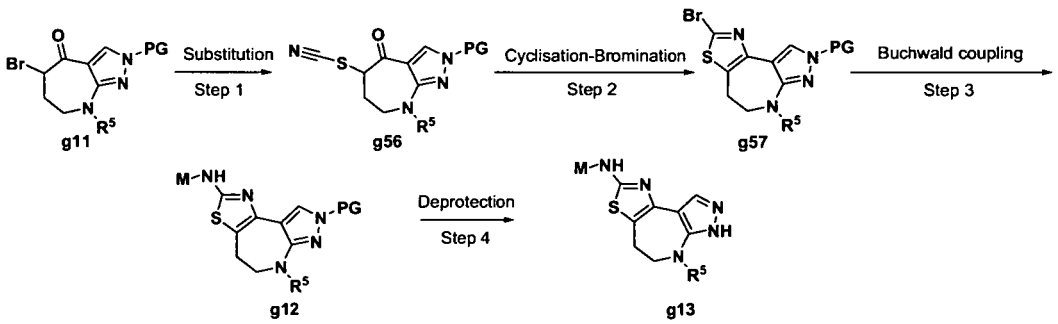
Scheme 14

In one embodiment of the present invention, compounds of Formula (III) may be prepared according to the synthetic sequences illustrated in Scheme 15. Compound **g29** can be alkylated by methylene-pyridinyl in the presence of a base such as K_2CO_3 and in a solvent such as NMP, to afford compound **g54**. The pyridine substituent of **g54** can be reduced by hydrogenation with $Pd(OH)_2$ and the resulting piperidine can be protected in situ due to the presence of Boc_2O. Finally, compound **g55** can afford compounds of Formula (III) using method described above.



Scheme 15

In one embodiment of the present invention, compounds of Formula (III) may be prepared according to the synthetic sequences illustrated in Scheme 16. Potassium thiocyanate can displace the halogen moiety in the α-bromoketone **g11** to afford compound **g56**. Then under acidic condition, compound **g56** can be cyclized into the 2-bromothiazole **g57** in the presence of a mixture of acetic acid and hydrobromic acid. The 2-bromothiazole **g57** can be coupled to heteroaryl amine M-NH_2, using Buchwald conditions with as a catalyst $Pd_2(dba)_3$ and the like, as a ligand Xantphos and the like and as a base Cs_2CO_3 to yield compound **g12** which can be finally deprotected under acidic conditions as described above to give compound **g13**.



Scheme 16

In general, substituted thiourea M-NH-(C=S)-NH_2 used in Schemes 1, 4, 10, 11 and 14, are prepared according to methods known by persons skilled in the art. For example, 5-fluoropyrimidin-2-amine can be reacted with ethyl carbonisothiocyanatidate in acetonitrile, then the resulting product can be treated with ammonium formate in ammonia affording the thiourea 5-fluoropyrimidin-2-yl-NH(C=S)-NH_2.

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.

ACN (Acetonitrile)	mg (Milligrams)
AcOH (Acetic acid)	$MgSO_4$ (Magnesium sulfate)
$AlMe_3$ (Trimethylaluminium)	min (Minutes)
atm (Atmosphere)	mL (Milliliters)
BBr_3 (Boron tribromide)	mmol (Millimoles)
BnBr (Benzyl bromide)	M.p. (Melting point)
BuLi (Butyl lithium)	NH_4Cl (Ammonium chloride)
t-BuOH (*tert*-Butanol)	$NaBH(OAc)_3$ (Sodium triacetoxyborohydride)
$CHCl_3$ (Chloroform)	NaH (Sodium hydride)
$CuBr_2$ (Copper (II) bromide)	$NaHCO_3$ (Sodium bicarbonate)
DCE (Dichloroethane)	NaI (Sodium iodide)
DCM (Dichloromethane)	Na_2CO_3 (Sodium carbonate)
DME (Dimethoxyethane)	Na_2SO_4 (Sodium sulfate)
DMF (Dimethylformamide)	NMP (*N*-Methylpyrrolidone)
EtOAc (Ethyl acetate)	$Pd(OAc)_2$ (Palladium(II)acetate)
EtOH (Ethanol)	$Pd(OH)_2$ (Palladium(II) hydroxide)
Et_2O (Diethyl ether)	$Pd_2(dba)_3$ (Tris(dibenzylideneacetone)dipalladium(0))
Et_3N (Triethylamine)	PE (Petroleum ether)
h (Hour)	Prep. HPLC (Preparative high pressure liquid chromatography)
HCl (Hydrochloric acid)	Prep. TLC (Preparative thin layer chromatography)
I_2 (Diiodine)	rt (Room temperature)
KO*t*Bu (Potassium *tert*-butoxide)	RT (Retention Time)
KOH (Potassium hydroxide)	TFA (Trifluoroacetic acid)
K_2CO_3 (Potassium carbonate)	TfOH (Trifluoromethane sulfonic acid)
LDA (Lithium diisopropylamide)	THF (Tetrahydrofuran)
LiHMDS (Lithium bis(trimethylsilyl)amide)	TLC (Thin layer chromatography)
LiOH (Lithium hydroxide)	UPLC-MS (Ultra Performance Liquid Chromatography Mass Spectrum)
M (Molar)	Xantphos (4,5-*Bis*(diphenylphosphino)-9,9-dimethylxanthene)
MeOH (Methanol)	

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 under an inert atmosphere at room temperature unless otherwise noted.

Most of the reactions 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 prepacked silica gel cartridges (15-40 μM, Merck).

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

^{1}H-NMR spectra were recorded on a Bruker 300 MHz or 400 MHz. Chemical shifts are expressed in parts per million (ppm, δ units). Coupling constants are in units of hertz (Hz) Splitting patterns describe apparent multiplicities and are designated as *s* (singlet), *d* (doublet), *t* (triplet), *q* (quadruplet), *m* (multiplet), *br* (broad).

EXAMPLES

EXAMPLE 1: 6-Methyl-*N*-(4-methylpyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo [3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (Final Compound 1-1)

Ethyl 1-(4-methoxybenzyl)-1H-pyrazole-4-carboxylate

According to Scheme 1, Step 1: A suspension of ethyl 1*H*-pyrazole-4-carboxylate (535 mmol, 75.0 g), 1-(chloromethyl)-4-methoxybenzene (562 mmol, 76 mL) and K_2CO_3 (803 mmol, 111 g) in ACN (750 mL) was heated under reflux for 4 h. At rt, the reaction mixture was filtered and concentrated under reduced pressure. The resulting yellow oil was triturated in petroleum ether and the precipitate isolated by filtration and dried under reduced pressure to yield the title compound (530 mmol, 138 g, 99%) as a white solid.

UPLC-MS: RT = 1.01 min; MS *m/z* ES^+= 261.

1-(4-Methoxybenzyl)-1H-pyrazole-4-carboxylic acid

According to Scheme 1, Step 2: A solution of LiOH (358 mmol, 15.3 g) in water (2 M) was added at rt to a solution of ethyl 1-(4-methoxybenzyl)-1*H*-pyrazole-4-carboxylate (143 mmol, 37.2 g) in THF/MeOH (1:1, 400 mL) and the reaction mixture was heated at 60°C overnight. After evaporation of the solvents, a solid was filtered, water (150 mL) was added and the aqueous phase was extracted with Et_2O. The aqueous phase was then acidified with a solution of HCl 1 M until pH = 1-2 and extracted with DCM. The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the title compound (138 mmol, 32.1 g, 97%) as a pale yellow solid. The crude product was used without further purification.

UPLC-MS: RT = 0.77 min; MS *m/z* ES^-= 231.

N-Methoxy-1-(4-methoxybenzyl)-N-methyl-1H-pyrazole-4-carboxamide

According to Scheme 1, Step 3: A solution of 1-(4-methoxybenzyl)-1*H*-pyrazole-4-carboxylic acid (34.4 mmol, 8.00 g), oxalyl chloride (68.9 mmol, 5.92 mL) and a drop of DMF in DCM (80 mL) was stirred for 1 h at rt. After evaporation, the crude product was dissolved in DCM (30 mL) and was added at 0°C to a solution of *N,O*-dimethylhydroxylamine hydrochloride (103 mmol, 6.31 g) in DCM (100 mL), followed by Et_3N (138 mmol, 19.2 mL). The reaction mixture was stirred for 1 h at rt. The reaction was quenched with a saturated aqueous solution of Na_2CO_3 (300 mL) and the aqueous phase was extracted with DCM. The organic layer was dried over $MgSO_4$, filtered and concentrated to dryness to yield the title compound (33.8 mmol, 9.30 g, 98%) as a beige solid.

UPLC-MS: RT = 0.72 min; MS *m/z* ES^+= 276.

3-Chloro-N-methoxy-1-(4-methoxybenzyl)-N-methyl-1H-pyrazole-4-carboxamide

According to Scheme 1, Step 4: BuLi 2.5 M (84 mmol, 34 mL) was added to a solution of diisopropylamine (84 mmol, 12 mL) in THF (100 mL) at -78°C and the reaction mixture was stirred at -78°C for 5 min and then at rt. The resulting LDA solution was added at -78°C to a solution of *N*-methoxy-1-(4-methoxybenzyl)-*N*-methyl-1*H*-

pyrazole-4-carboxamide (36.3 mmol, 10.0 g) in THF (30 mL) and the reaction mixture was stirred for 5 min at -78°C. Then a solution of hexachloroethane (84.0 mmol, 19.9 g) in THF (30 mL) was added to the black reaction mixture at -78°C. The solution was stirred for 5 min at -78°C and for 1 h at rt. The reaction mixture was quenched with water (50 mL) and the aqueous phase was extracted with EtOAc. The organic phase was dried over $MgSO_4$, was filtered and was concentrated to give a brown oil. The resulting crude product was purified by flash chromatography over silica gel using cyclohexane/EtOAc (100:0 to 50:50) as eluent to yield after evaporation the title compound (16 mmol, 5.0 g, 42%) as a beige solid.

UPLC-MS: RT = 0.85 min; MS *m/z* ES^+= 310.

N-Methoxy-1-(4-methoxybenzyl)-N-methyl-3-(methylamino)-1H-pyrazole-4-carboxamide

According to Scheme 1, Step 5: A solution of 3-chloro-*N*-methoxy-1-(4-methoxybenzyl)-*N*-methyl-1*H*-pyrazole-4-carboxamide (3.23 mmol, 1.00 g) and methanamine hydrate (32.3 mmol, 4.00 mL) in NMP (10 mL) was heated in the microwave at 140°C for 1.5 h. The reaction was diluted with EtOAc and the organic layer was washed with water, dried over $MgSO_4$, filtered and concentrated to dryness. The crude compound was purified by flash chromatography with silica gel using cyclohexane/EtOAc (10:0 to 5:5) as eluent to yield the title compound (1.81 mmol, 550 mg, 56%).

UPLC-MS: RT = 0.79 min; MS *m/z* ES^+= 305.

3-(Allyl(methyl)amino)-N-methoxy-1-(4-methoxybenzyl)-N-methyl-1H-pyrazole-4-carboxamide

According to Scheme 1, Step 6: To a solution of *N*-methoxy-1-(4-methoxybenzyl)-*N*-methyl-3-(methylamino)-1*H*-pyrazole-4-carboxamide (1.64 mmol, 500 mg) in THF/DMF (5 mL; 1:1) was added portionwise NaH (3.28 mmol, 131 mg, 60%) and the reaction mixture was stirred for 45 min at rt. 3-Bromoprop-1-ene (4.11 mmol, 350 µL) was then added and the solution was stirred for 2 h at 65°C. The solution was

concentrated, was dissolved with DCM and was washed with a saturated solution of Na_2CO_3. The organic layer was dried over $MgSO_4$, filtered and concentrated to dryness. The crude compound was purified by flash chromatography with silica gel using DCM/MeOH (98:2) as eluent to yield the title compound (0.90 mmol, 310 mg, 55%).

UPLC-MS: RT = 0.98 min; MS *m/z* ES^+= 345.

1-(3-(Allyl(methyl)amino)-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)prop-2-en-1-one

According to Scheme 1, Step 7: Under a nitrogen atmosphere, vinylmagnesium bromide (2.70 mmol, 354 mg) was added to a solution of 3-(allyl(methyl)amino)-*N*-methoxy-1-(4-methoxybenzyl)-*N*-methyl-1*H*-pyrazole-4-carboxamide (0.90 mmol, 310 mg) in THF (10 mL), and the resulting solution was stirred for 15 min at rt. Some more vinylmagnesium bromide (2.70 mmol, 236 mg) was added to complete the reaction. Then the reaction mixture was quenched with water and the aqueous phase was extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated to dryness. The crude compound was purified by flash chromatography with silica gel using cylohexane/EtOAc (100:0 to 70:30) as eluent to yield the title compound (0.87 mmol, 250 mg, 89%).

UPLC-MS: RT = 1.09 min; MS m/z ES^+= 312.

(Z)-2-(4-Methoxybenzyl)-8-methyl-7,8-dihydropyrazolo[3,4-b]azepin-4(2H)-one

According to Scheme 1, Step 8: Under a nitrogen atmosphere, Grubbs catalyst 2nd generation (benzylidene[1,3- *bis*(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro (tricyclohexylphosphine)ruthenium; 0.08 mmol, 68.3 mg) was added to a solution of 1-(3-(allyl(methyl)amino)-1-(4-methoxybenzyl)-1*H*-pyrazol-4-yl)prop-2-en-1-one (0.80 mmol, 250 mg) in DCM (110 mL) and the solution was stirred for 1 h under reflux. The reaction mixture was evaporated to dryness. The crude compound was purified by flash chromatography with silica gel using DCM/MeOH (100:0 to 97:3) as eluent to yield the title compound (0.76 mmol, 215 mg, 95%).

UPLC-MS: RT = 0.8 min; MS m/z ES^+= 284.

2-(4-Methoxybenzyl)-8-methyl-5,6,7,8-tetrahydropyrazolo[3,4-b]azepin-4(2H)-one

According to Scheme 1, Step 9: A mixture of (*Z*)-2-(4-methoxybenzyl)-8-methyl-7,8-dihydropyrazolo[3,4-*b*]azepin-4(2*H*)-one (0.76 mmol, 215 mg), ammonium formate (7.59 mmol, 478 mg) and $Pd(OH)_2$ (0.15 mmol, 21.3 mg) in MeOH (8 mL) was stirred under reflux for 2 h. The reaction mixture was filtered through celite pad and was washed with MeOH. The filtrate was concentrated to dryness then dissolved with EtOAc and was washed with a saturated aqueous solution of Na_2CO_3. The organic layer was dried over $MgSO_4$, filtered and concentrated to dryness to yield the title compound (0.70 mmol, 200 mg, 92%).

UPLC-MS: RT = 0.79 min; MS m/z ES^+= 286.

5-Bromo-2-(4-methoxybenzyl)-8-methyl-5,6,7,8-tetrahydropyrazolo[3,4-b]azepin-4(2H)-one

According to Scheme 1, Step 10: To a solution of 2-(4-methoxybenzyl)-8-methyl-5,6,7,8-tetrahydropyrazolo[3,4-*b*]azepin-4(2*H*)-one (0.70 mmol, 200 mg) in MeOH (7 mL) was added $CuBr_2$ (2.10 mmol, 470 mg) and the solution was heated under reflux for 2 h. After evaporation, the crude residue was dissolved in DCM and the organic phase was washed with a saturated aqueous solution of Na_2CO_3. The organic layer was dried over $MgSO_4$, filtered and concentrated to dryness. The crude compound was purified by flash chromatography with silica gel using DCM/MeOH (100:0 to 97:3) as eluent to yield the title compound (0.56 mmol, 205 mg, 80%).

UPLC-MS: RT = 0.91 min; MS m/z ES^+= 364.

8-(4-Methoxybenzyl)-6-methyl-N-(4-methylpyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo [3,4-b]thiazolo[4,5-d]azepin-2-amine

According to Scheme 1, Step 11: A mixture of 5-bromo-2-(4-methoxybenzyl)-8-methyl-5,6,7,8-tetrahydropyrazolo[3,4-*b*]azepin-4(2*H*)-one (0.27 mmol, 100 mg) and 1-(4-methylpyrimidin-2-yl)thiourea (0.27 mmol, 46.2 mg) in EtOH (5 mL) was heated under reflux overnight. Then the solution was concentrated to dryness, the residue was solubilised in EtOAc and the organic phase was washed with a saturated aqueous solution of Na_2CO_3. The organic layer was dried over $MgSO_4$, filtered and concentrated to dryness. The crude compound was purified by flash chromatography with silica gel

using cyclohexane/EtOAc (100:0 to 0:100) as eluent to yield the title compound (0.10 mmol, 45 mg, 38%).

UPLC-MS: RT = 1.06 min; MS m/z ES^+= 434.

6-Methyl-N-(4-methylpyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-b]thiazolo[4,5-d] azepin-2-amine

According to Scheme 1, Step 12, Method A: Trifluoromethanesulfonic acid (0.52 mmol, 78 mg) was added to a solution of 8-(4-methoxybenzyl)-6-methyl-*N*-(4-methylpyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (0.10 mmol, 45 mg) in TFA (100 µL). The reaction mixture was stirred at rt for 15 min. The solution was quenched with water and extracted with EtOAc. The organic layer was dried over $MgSO_4$, was filtered and was concentrated. The crude compound was purified by flash chromatography with silica gel using DCM/MeOH (100:0 to 94:6) as eluent to yield the title compound (48 µmol, 15mg, 46%) as a white powder.

UPLC-MS: RT = 0.72 min; MS m/z ES^+= 314.

^{1}H-NMR (300 MHz, DMSO-d_6): 12.0 (s, 1H), 11.3 (s, 1H), 8.4 (d, 1H), 7.6 (s, 1H), 6.95 (d, 1H), 3.3 (m, 2H), 3.05(m, 2H), 2.95(s, 3H), 2.45 (s, 3H).

EXAMPLE 2: 6-Isopropyl-*N*-(4-methylpyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo [3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (Final Compound 1-5)

According to Scheme 1, Step 12, Method B: A solution of 6-isopropyl-8-(4-methoxybenzyl)-*N*-(4-methylpyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo [4,5-*d*]azepin-2-amine (118 mg, 0.26 mmol, synthesized as in Scheme 1) in TFA (3 mL) was stirred at 60°C for 1 h. TFA was evaporated under reduced pressure to afford a yellow solid. The crude solid was dissolved in EtOAc. The organic layer was washed twice with a saturated Na_2CO_3 solution, once with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel using DCM/MeOH (96:4) as eluent to yield the title compound (82 µmol, 28 mg, 32%) as a yellow solid.

UPLC-MS: RT = 0.85 min; MS m/z ES^+= 342;

^{1}H-NMR (300 MHz, DMSO-d_6): 8.43 (1H, d, 5Hz), 7.67 (1H, s), 6.88 (1H, d, 5Hz), 3.34 (1H, m), 3.20-3.17 (2H, m), 2.99-2.95 (2H, m), 2.42 (3H, s), 1.14 (6H, d, 6.7Hz).

EXAMPLE 3: *N*-(5-Fluoropyrimidin-2-yl)-6-methyl-4,5,6,8-tetrahydropyrazolo [3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (Final Compound 1-2)

8-(4-Methoxybenzyl)-6-methyl-4,5,6,8-tetrahydropyrazolo[3,4-b]thiazolo[4,5-d]azepin-2-amine

According to Scheme 2, Step 1: A mixture of 5-bromo-2-(4-methoxybenzyl)-8-methyl-5,6,7,8-tetrahydropyrazolo[3,4-*b*]azepin-4(2*H*)-one (0.27 mmol, 100 mg, synthesized as in Scheme 1) and thiourea (0.27 mmol, 21 mg) in EtOH (3 mL) was heated under reflux overnight. After evaporation, the crude compound was dissolved EtOAc and the organic phase was washed with a saturated aqueous solution of Na_2CO_3. The organic layer was dried over $MgSO_4$, filtered and concentrated to dryness. The crude compound was purified by flash chromatography with silica gel using cyclohexane/EtOAc (100:0 to 0:100) as eluent to yield the title compound (0.13 mmol, 45 mg, 48%).

UPLC-MS: RT = 0.68 min; MS m/z ES^+= 342.

N-(5-Fluoropyrimidin-2-yl)-8-(4-methoxybenzyl)-6-methyl-4,5,6,8-tetrahydropyrazolo [3,4-b]thiazolo[4,5-d]azepin-2-amine

According to Scheme 2, Step 2: A mixture of 8-(4-methoxybenzyl)-6-methyl-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (0.13 mmol, 45 mg), 2-chloro-5-fluoropyrimidine (0.20 mmol, 26.2 mg), sodium 2-methylpropan-2-olate (0.13 mmol, 12.7 mg), (*R*)-(-)-1-[(*S*)-2-(dicyclohexylphosphino)ferrocenyl]ethyldi-*t*-butylphosphine (13 µmol, 7.3 mg) and $Pd(OAc)_2$ (13 µmol, 3.0 mg) in DME (1.3 mL) was heated in the microwave at 120°C for 2 h. After evaporation, the crude residue was purified by flash chromatography with silica gel using DCM/MeOH (100:0 to 97:3) to yield the title compound (0.10 mmol, 45mg, 78%).

UPLC-MS: RT = 1.06 min; MS m/z ES^+= 438.

N-(5-Fluoropyrimidin-2-yl)-6-methyl-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*] azepin-2-amine (47 µmol, 15mg, 46%) was obtained as a beige solid following the same experimental part as described for Example 1, Step 12, Method A.

UPLC-MS: RT = 1.06 min; MS m/z ES^+= 318;

^{1}H-NMR (300 MHz, DMSO-d_6): 11.8 (s, 1H), 8.7 (s, 2H), 7.7 (s, 1H), 3.3 (m, 2H), 3.0 (m, 2H), 2.9 (s, 3H).

EXAMPLE 4: 6-(Cyclopropylmethyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,8-tetra hydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (Final Compound 1-4)

According to Scheme 2, Step 3, Method B: 6-(Cyclopropylmethyl)-*N*-(5-fluoropyrimidin-2-yl)-8-(4-methoxybenzyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo [4,5-*d*]azepin-2-amine (45 mg, 94 µmol, synthesized as in Scheme 2) was dissolved into TFA. The solution was stirred at rt for 15 min and then at 60°C for 1 h. The mixture was diluted with water and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel using DCM/MeOH (100:0 to 94:6) as eluent to yield the title compound (17 µmol, 6 mg, 18%) as a beige solid.

UPLC-MS: RT = 0.92 min; MS m/z ES^+= 358;

^{1}H-NMR (300 MHz, DMSO-d_6): 12.0 (s, 1H), 11.3 (s, 1H) 8.7 (s, 2H), 7.6 (s, 1H), 3.4 (m, 2H), 3.1 (m, 2H), 2.95 (m, 2H), 2.45 (s, 3H).

EXAMPLE 5: 6-(2-Methoxyethyl)-*N*-(6-methylpyridin-2-yl)-4,5,6,8-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (Final Compound 1-13)

6-(2-Methoxyethyl)-4,5,6,8-tetrahydropyrazolo[3,4-b]thiazolo[4,5-d]azepin-2-amine

According to Scheme 3, Step 1: The title compound was obtained using the same procedure as described in Scheme 2, Step 3, Method B with 8-(4-methoxybenzyl)-6-(2-methoxyethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (184 mg, 0.48 mmol, synthesized as in Scheme 2) in TFA (2.5 mL) to yield 6-(2-

methoxyethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (294 μmol, 78 mg, 62%).

UPLC-MS: RT = 0.40-0.44 min; MS m/z ES^+= 266.

6-(2-Methoxyethyl)-N-(6-methylpyridin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-b] thiazolo[4,5-d]azepin-2-amine

According to Scheme 3, Step 2: A mixture of 6-(2-methoxyethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (40 mg, 0.15 mmol), 2-bromo-6-methylpyridine (34 μL, 302 μmol), sodium 2-methylpropan-2-olate (21.7 mg, 226 μmol), $Pd_2(dba)_3$ (13.8 mg, 15 μmol) and Xantphos (17.4 mg, 30 μmol) in toluene (1.5 mL) was stirred at 90°C for 30 min. The mixture was diluted with EtOAc. The organic layer was washed first with a saturated K_2CO_3 solution and then with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a brown residue. The crude residue was purified by preparative HPLC to yield the title compound (8 μmol, 3 mg, 6%) as as brown solid.

UPLC-MS: RT = 0.68 min; MS m/z ES^+= 357;
^{1}H-NMR (300 MHz, $CDCl_3$): 8.59 (1H, s), 8.04 (1H, s), 7.51 (1H, m), 6.81-6.74 (2H, m), 3.98 (3H, s), 3.68-3.61 (4H, m), 3.53-3.49 (2H, m), 3.07-3.04 (2H, m), 2.54 (3H, s).

EXAMPLE 6: *N*-(5-Fluoropyrimidin-2-yl)-6-(pyridin-2-ylmethyl)-4,5,6,8-tetra hydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (Final Compound 1-26)

2-(4-Methoxybenzyl)-8-(pyridin-2-ylmethyl)-5,6,7,8-tetrahydropyrazolo[3,4-b]azepin-4(2H)-one

According to Scheme 8, Step 6, Method B: To a solution of 2-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrazolo[3,4-*b*]azepin-4(2*H*)-one (300 mg, 1.11 mmol, synthesized as in Scheme 7) in THF (6 mL) was added LiHMDS (1.25 mL, 1.33 mmol) and the reaction mixture was stirred at rt for 30 min. In another flask, K_2CO_3 (458 mg, 3.32 mmol) was added to a solution of 2-(bromomethyl)pyridine hydrobromide (559 mg, 2.21 mmol) in DMF (6 mL) and the reaction mixture was stirred for 30 min. The latter solution was added to the initial reaction mixture. The resulting mixture was stirred at rt

for 45 min. After evaporation of the solvents, water was added to the residue and the aqueous layer was extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by preparative HPLC to yield the title compound (157 µmol, 57 mg, 14%).

UPLC-MS: RT = 0.70 min; MS m/z ES^+= 363.

N-(5-Fluoropyrimidin-2-yl)-8-(4-methoxybenzyl)-6-(pyridin-2-ylmethyl)-4,5,6,8-tetrahydropyrazolo[3,4-b]thiazolo[4,5-d]azepin-2-amine

According to Scheme 4, Step 1: A solution of 2-(4-methoxybenzyl)-8-(pyridin-2-ylmethyl)-5,6,7,8-tetrahydropyrazolo[3,4-*b*]azepin-4(2*H*)-one (57 mg, 157 µmol), (5-fluoropyrimidin-2-yl)thiourea (32.5 mg, 189 µmol) and I_2 (39.9 mg, 157 µmol) in pyridine (315 µl) was stirred at 90°C for 4 h. After dilution with water of the reaction mixture, the aqueous layer was extracted twice with DCM. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the title compound (39 µmol, 20 mg, 25%).

UPLC-MS: RT = 0.94 min; MS m/z ES^+= 515.

N-(5-Fluoropyrimidin-2-yl)-6-(pyridin-2-ylmethyl)-4,5,6,8-tetrahydropyrazolo[3,4-b] thiazolo[4,5-d]azepin-2-amine

According to Scheme 4, Step 2: The title compound was obtained using the same procedure as described in Scheme 1, Step 12, Method B with *N*-(5-fluoropyrimidin-2-yl)-8-(4-methoxybenzyl)-6-(pyridin-2-ylmethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine (20 mg, 39 µmol) in TFA (2 mL) to yield *N*-(5-fluoropyrimidin-2-yl)-6-(pyridin-2-ylmethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo [4,5-*d*]azepin-2-amine (8 µmol, 3.2 mg, 21%) as a brown solid.

UPLC-MS: RT = 0.62 min; MS m/z ES^+= 395.
^{1}H-NMR (300 MHz, CD_3OD): 8.5 (2H, s), 8.5 (1H, m), 7.9 (1H, m), 7.8 (1H, m), 7.5 (1H, m), 7.4 (1H, m), 4.7 (2H, s), 3.4 (2H, m), 3.0 (2H, m).

EXAMPLE 7: 6-((1-Methyl-1*H*-pyrazol-3-yl)methyl)-*N*-(4-methylpyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (Final Compound 1-16)

Ethyl 3-amino-1-(4-methoxybenzyl)-1H-pyrazole-4-carboxylate

According to Scheme 5 Step 1: 1-(Chloromethyl)-4-methoxybenzene (12.9 mmol, 2.02 g) followed by K_2CO_3 (25.8 mmol, 3.56 g) were added to a solution of ethyl 3-amino-1*H*-pyrazole-4-carboxylate (12.9 mmol, 2.00 g) in ACN (10 mL) and then the reaction mixture was heated at 60°C for 3 h. After evaporation of the solvent, a saturated solution of Na_2CO_3 was added and the aqueous phase was extracted with AcOEt. 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 (100:0 to 20:80) as eluent to afford ethyl 3-amino-1-(4-methoxybenzyl)-1*H*-pyrazole-4-carboxylate (6.90 mmol, 1.90 g, 53%) as a white powder.

UPLC-MS: RT = 0.82 min; MS *m/z* ES^+= 276.

Ethyl 1-(4-methoxybenzyl)-3-((1-methyl-1H-pyrazol-3-yl)methylamino)-1H-pyrazole-4-carboxylate

According to Scheme 5, Step 2: To a solution of ethyl 3-amino-1-(4-methoxybenzyl)-1*H*-pyrazole-4-carboxylate (573 mg, 2.08 mmol) in DCM (20 mL) was added 1-methyl-1H-pyrazole-3-carbaldehyde (229 mg, 2.08 mmol) and AcOH (5.96 mL, 104 mmol). After cooling the reaction mixture to 0°C, $NaBH(OAc)_3$ (882 mg, 4.16 mmol) was added portionwise and the reaction mixture was stirred at rt for 1 day. The mixture was quenched with an aqueous $NaHCO_3$ solution. The aqueous layer was extracted 3 times with DCM. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel using cyclohexane/EtOAc (100:0 to 0:100) as eluent to yield the title compound (0.73 mmol, 270 mg, 35%).

UPLC-MS: RT = 0.92 min; MS m/z ES^+= 370.

Ethyl 3-(allyl((1-methyl-1H-pyrazol-3-yl)methyl)amino)-1-(4-methoxybenzyl)-1H-pyrazole-4-carboxylate

According to Scheme 5, Step 3: The title compound was obtained using the same procedure as described in Scheme 1, Step 6 with ethyl 1-(4-methoxybenzyl)-3-((1-methyl-1*H*-pyrazol-3-yl)methylamino)-1*H*-pyrazole-4-carboxylate (220 mg, 0.60 mmol), NaH (71.5 mg, 1.79 mmol, 60%) and 3-bromoprop-1-ene (0.10 mL, 1.19 mmol) in THF/DMF (1:1, 2 mL) to yield ethyl 3-(allyl((1-methyl-1*H*-pyrazol-3-yl)methyl)amino)-1-(4-methoxybenzyl)-1*H*-pyrazole-4-carboxylate (0.49 mmol, 200 mg, 82%).

UPLC-MS: RT = 1.07 min; MS m/z ES^+= 411.

3-(Allyl((1-methyl-1H-pyrazol-3-yl)methyl)amino)-1-(4-methoxybenzyl)-1H-pyrazole-4-carboxylic acid

According to Scheme 5, Step 4: To a solution of ethyl 3-(allyl((1-methyl-1*H*-pyrazol-3-yl)methyl)amino)-1-(4-methoxybenzyl)-1*H*-pyrazole-4-carboxylate (200 mg, 0.49 mmol) in MeOH/water (3:1, 12 mL) was added LiOH (58.5 mg, 2.44 mmol) and the reaction mixture was stirred at 80°C for 2 h. Then MeOH was evaporated and water was added to the residue. The aqueous layer was acidified to pH=5 with 1N HCl and extracted 3 times with DCM. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the title compound (0.37 mmol, 140 mg, 75%).

UPLC-MS: RT = 0.84 min; MS m/z ES^+= 382.

3-(Allyl((1-methyl-1H-pyrazol-3-yl)methyl)amino)-N-methoxy-1-(4-methoxybenzyl)-N-methyl-1H-pyrazole-4-carboxamide

According to Scheme 5, Step 5: The title compound was obtained using the same procedure as described in Scheme 1, Step 3 with 3-(allyl((1-methyl-1*H*-pyrazol-3-yl)methyl)amino)-1-(4-methoxybenzyl)-1*H*-pyrazole-4-carboxylic acid (140 mg, 0.37 mmol), oxalyl dichloride (63.0 µl, 734 µmol), a drop of DMF, Et_3N (133 µl, 954 µmol) and *N,O*-dimethylhydroxylammonium chloride (53.7 mg, 551 µmol) to yield 3-

(allyl((1-methyl-1*H*-pyraz,ol-3-yl)methyl)amino)-*N*-methoxy-1-(4-methoxybenzyl)-*N*-methyl-1*H*-pyrazole-4-carboxamide (236 µmol, 100 mg, 64%).

UPLC-MS: RT = 0.87 min; MS m/z ES^+= 426.

6-((1-Methyl-1*H*-pyrazol-3-yl)methyl)-*N*-(4-methylpyrimidin-2-yl)-4,5,6,8-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (3 µmol, 1.2 mg, 26%) was obtained as a yellow solid following the same experimental part as described for Example 1 from Step 7 until Step 12, Method A.

UPLC-MS: RT = 0.74 min; MS m/z ES^+= 394;

^{1}H-NMR (300 MHz, CD_3OD): 8.4 (1H, d, 4.8Hz), 7.85 (1H, s), 7.5 (1H, d, 2.3Hz), 6.8 (1H, d, 4.8Hz), 6.2 (1H, d, 2.3Hz), 4.5 (2H, s), 3.85 (3H, s), 3.35 (2H, m), 2.95 (2H, m), 2.45 (3H, s).

EXAMPLE 8: *N*-(5-Fluoropyrimidin-2-yl)-6-(3,3,3-trifluoropropyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (Final Compound 1-29)

3-Amino-N-methoxy-1-(4-methoxybenzyl)-N-methyl-1H-pyrazole-4-carboxamide

According to Scheme 6, Step 1: Under nitrogen, a solution of ethyl 3-amino-1-(4-methoxybenzyl)-1*H*-pyrazole-4-carboxylate (3.00 g, 10.9 mmol, synthesized as in Scheme 5) in DCM (50 mL) was stirred at 0°C. $AlMe_3$ (6.28 g, 87.0 mmol) was added dropwise at 0°C and the solution was stirred at 0°C for 20 min and at rt for 20 min. After cooling the reaction mixture to 0°C, *N,O*-dimethylhydroxylamine hydrochloride (4.25 g, 43.6 mmol) was added dropwise at 0°C and the mixture was stirred at rt for 10 min and at reflux for 5 h. The mixture was slowly quenched with water and extracted 2 times with DCM. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel using cyclohexane/EtOAc (50:50 to 0:100) as eluent to yield the title compound (6.20 mmol, 1.80 g, 57%).

UPLC-MS: RT = 0.71 min; MS m/z ES^+= 291.

N-Methoxy-1-(4-methoxybenzyl)-N-methyl-3-(3,3,3-trifluoropropylamino)-1H-pyrazole -4-carboxamide

According to Scheme 6, Step 2: The title compound was obtained using the same procedure as described in Scheme 4, Step 1 with 3-amino-*N*-methoxy-1-(4-methoxybenzyl)-*N*-methyl-1*H*-pyrazole-4-carboxamide (720 mg, 2.48 mmol), AcOH (8 mL), 3,3,3-trifluoropropanal (834 mg, 7.44 mmol) and $NaBH(OAc)_3$ (2,10 g, 9.92 mmol) in DCM (20 mL) to yield *N*-methoxy-1-(4-methoxybenzyl)-*N*-methyl-3-(3,3,3-trifluoropropylamino)-1*H*-pyrazole-4-carboxamide (1.82 mmol, 705 mg, 74%).

UPLC-MS: RT = 1.02 min; MS m/z ES^+= 387.

3-(Allyl(3,3,3-trifluoropropyl)amino)-N-methoxy-1-(4-methoxybenzyl)-N-methyl-1H-pyrazole-4-carboxamide

According to Scheme 6, Step 3: To a solution of *N*-methoxy-1-(4-methoxybenzyl)-*N*-methyl-3-(3,3,3-trifluoropropylamino)-1*H*-pyrazole-4-carboxamide (580 mg, 1.50 mmol) in THF (25 mL) was added LiHMDS (502 mg, 3.00 mmol) and the reaction mixture was stirred at rt for 15 min. Then 3-bromoprop-1-ene (363 mg, 3.00 mmol) was added and the reaction mixture was stirred at reflux for 1 h. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel using cyclohexane/EtOAc (100:0 to 40:60) as eluent to yield the title compound (1.01 mmol, 430 mg, 67%).

UPLC-MS: RT = 1.12 min; MS m/z ES^+= 427.

N-(5-fluoropyrimidin-2-yl)-6-(3,3,3-trifluoropropyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (24 µmol, 9.6 mg, 25%) was obtained as a beige solid following the same experimental part as described in the Scheme 1 from Steps 7 to 9, then Scheme 4 Step 1 and finally Scheme 1 Step 12, Method B.

UPLC-MS: RT = 0.98 min; MS m/z ES^+= 400;

^{1}H-NMR (300 MHz, DMSO-d_6): 11.7(s, 1H), 8.7 (s, 2H), 7.7 (s, 1H), 3.5 (m, 4H), 3.4(m, 2H), 3.0 (m, 2H).

EXAMPLE 9: *N*-(4-Methylpyrimidin-2-yl)-6-((tetrahydrofuran-2-yl)methyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine **(Final Compound 1-10)**

Ethyl 5-[(4-ethoxy-4-oxobutyl)amino]-1-(4-methoxybenzyl)-1H-pyrazole-4-carboxylate

According to Scheme 7, Step 1: To a suspension of ethyl 5-amino-1-(4-methoxybenzyl)-1*H*-pyrazole-4-carboxylate (50.0 g, 180 mmol) and K_2CO_3 (49.0 g, 360 mmol) in NMP (700 mL) was added 4-bromo-butyric acid ethyl ester (140 g, 720 mmol), and the mixture was heated at 120°C for 36 h. After cooling to rt, water (500 mL) was added to the mixture and it was extracted with EtOAc (200 mL×3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (PE : EtOAc = 20:1 to 7:1) to give the title product (58 g, 83%).

MS (ESI) *m/z* 390 **$(M+H)^+$**

Ethyl 5-[benzyl(4-ethoxy-4-oxobutyl)amino]-1-(4-methoxybenzyl)-1H-pyrazole-4-carboxylate

According to Scheme 7, Step 2: To a suspension of ethyl 5-[(4-ethoxy-4-oxobutyl)amino]-1-(4-methoxybenzyl)-1*H*-pyrazole-4-carboxylate (10 g, 26 mmol) and K_2CO_3 (8.9 g, 64 mmol) in NMP (100 mL) was added BnBr (5.7 g, 33 mmol). The mixture was heated at 140°C for 6 h. Water (100 mL) was added and the mixture was extracted with EtOAc (80 mL×3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography (PE : EtOAc = 20:1 to 6:1) to give the title product (10.0 g, 81%).

MS (ESI) *m/z* 480 **$(M+H)^+$**

Ethyl 8-benzyl-1-(4-methoxybenzyl)-4-oxo-1,4,5,6,7,8-hexahydropyrazolo[3,4-b]azepine-5-carboxylate

According to Scheme 7, Step 3: To a solution of ethyl 5-[benzyl(4-ethoxy-4-oxobutyl)amino]-1-(4-methoxybenzyl)-1*H*-pyrazole-4-carboxylate (10.0 g, 21.0 mmol) in THF (100 mL) was added LiHMDS (1.0 M in THF, 52 mL, 52 mmol) at 0 °C, then

the solution was stirred at 70°C for 1.5 h. Water (100 mL) was added and the mixture was extracted with EtOAc (80 mL×3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to get the title product (8.2 g, 91%).

MS (ESI): ***m/z*** 434 $(M+H)^+$;

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.63 (s, 1H), 7.21-7.29 (m, 4H), 7.13-7.18 (m, 3H), 6.80 (d, *J* = 8.0 Hz, 2H), 4.92-4.96 (m, 2H), 4.48-4.62 (m, 2H), 4.07-4.14 (m, 2H), 3.73 (s, 3H), 3.51-3.55 (m, 1H), 3.16-3.24 (m, 2H), 2.57-2.59 (m, 1H), 2.11-2.24 (m, 1H), 1.15-1.21 (m, 3H).

8-Benzyl-1-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrazolo[3,4-b]azepin-4(1H)-one

According to Scheme 7, Step 4: A suspension of ethyl 8-benzyl-1-(4-methoxybenzyl)-4-oxo-1,4,5,6,7,8-hexahydropyrazolo[3,4-*b*]azepine-5-carboxylate (8.2 g, 19 mmol) and KOH (2.6 g, 47 mmol) in ethylene glycol (90 mL) was heated at 110°C for 1 h. Water (100 mL) was added and the mixture was extracted with EtOAc (80 mL×3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give the title product (6.2 g, 93%).

MS (ESI) *m/z* 362 $(M+H)^+$;

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.61 (s, 1H), 7.20-7.24 (m, 4H), 7.14-7.18 (m, 3H), 6.80 (d, *J* = 8.8 Hz, 2H), 4.92 (s, 2H), 4.58 (s, 2H), 3.74 (s, 3H), 3.19-3.22 (m, 2H), 2.54-2.57 (m, 2H), 1.88-1.93 (m, 2H).

1-(4-Methoxybenzyl)-5,6,7,8-tetrahydropyrazolo[3,4-b]azepin-4(1H)-one

According to Scheme 7, Step 5: To a solution of 8-benzyl-1-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrazolo[3,4-*b*]azepin-4(1*H*)-one (5.8 g, 16 mmol) in EtOH (60 mL) and AcOH (60 mL) was added to $Pd(OH)_2$ (600 mg), then the mixture was stirred at 50 °C under H_2 (50 Psi) for 2 h. The mixture was filtered through Celite, and the filtrate was concentrated. The residue was purified by silica gel chromatography (PE:EtOAc, 10:1 to 1:1) to give the title product (2.5 g, 57%).

MS (ESI) *m/z* 272 $(M+H)^+$;

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.63 (s, 1H), 7.18 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 4.94 (s, 2H), 3.78 (s, 3H), 3.37-3.39 (m, 2H), 2.66-2.69 (m, 2H), 1.97-2.02 (m, 2H).

1-(4-Methoxybenzyl)-8-(tetrahydrofuran-2-ylmethyl)-5,6,7,8-tetrahydropyrazolo[3,4-b]azepin-4(1H)-one

According to Scheme 7, Step 6: A solution of 1-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrazolo[3,4-*b*]azepin-4(1*H*)-one (2.0 g, 7.4 mmol), and K_2CO_3 (2.4 g, 15 mmol) in 2-bromomethyltetrahydrofuran (20 mL) was stirred at 120°C for 48 h. After cooling to rt, the mixture was filtered and concentrated to give the crude desired product, which was purified by chromatography on silica (PE : EtOAc = 10: 1 to 1:1) to give the title product (800 mg, 30%).

MS (ESI): ***m/z*** 356 $(M+H)^+$

5-Bromo-1-(4-methoxybenzyl)-8-(tetrahydrofuran-2-ylmethyl)-5,6,7,8-tetrahydro pyrazolo[3,4-b]azepin-4(1H)-one

According to Scheme 1, Step 10: A mixture of 1-(4-methoxybenzyl)-8-(tetrahydrofuran-2-ylmethyl)-5,6,7,8-tetrahydropyrazolo[3,4-*b*]azepin-4(1*H*)-one (800 mg, 2.20 mmol) and trimethylphenylammomium tribromide (847 mg, 2.20 mmol) in $CHCl_3$ (15 mL) was refluxed for 1 h. After the reaction was finished, the mixture was washed with water (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title product (850 mg, 89%), which was used for the next step without further purification.

MS (ESI) *m/z* 434,436 $(M+H)^+$

7-(4-Methoxybenzyl)-N-(4-methylpyrimidin-2-yl)-6-(tetrahydrofuran-2-ylmethyl)-4,5,6,7-tetrahydropyrazolo[3,4-b][1,3]thiazolo[4,5-d]azepin-2-amine

According to Scheme 1, Step 11: A mixture of 5-bromo-1-(4-methoxybenzyl)-8-(tetrahydrofuran-2-ylmethyl)-5,6,7,8-tetrahydropyrazolo[3,4-*b*]azepin-4(1*H*)-one (850

mg, 2.00 mmol) and (4-methyl-pyrimidin-2-yl)thiourea (396 mg, 2.40 mmol) in *t*-BuOH (10 mL) and acetone (1 mL) was refluxed for 17 h. After the reaction was completed, the mixture was filtered and concentrated under reduced pressure. The residue was purified by recrystallization to give the title product (700 mg, 71%).

MS (ESI) *m/z* 503 **$(M+H)^+$**

N-(4-Methylpyrimidin-2-yl)-6-((tetrahydrofuran-2-yl)methyl)-4,5,6,8-tetrahydro pyrazolo[3,4-b]thiazolo[4,5-d]azepin-2-amine

According to Scheme 1, Step 12, Method A: A solution of 7-(4-methoxybenzyl)-*N*-(4-methylpyrimidin-2-yl)-6-(tetrahydrofuran-2-ylmethyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*][1,3]thiazolo[4,5-*d*]azepin-2-amine (700 mg, 1.4 mmol) in TFA (10 mL) and TfOH (1 mL) was stirred at 100 °C for 1.5 h. The mixture was concentrated in vacuo, and then DCM:MeOH (10:1) was added. The solution was basified with K_2CO_3, then filtered and concentrated. The residue was purified by Prep.TLC (DCM:MeOH = 10:1), and Prep-HPLC to yield the title product (103 mg, 19%).

MS (ESI): *m/z* 384 **$(M+H)^+$;**

^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.76 (s, 1H), 11.31 (s, 1H), 8.38 (d, *J* = 4.8 Hz, 1H), 7.26 (s, 1H), 6.83 (d, *J* = 4.8 Hz, 1H), 4.09 (s, 1H), 3.73 (t, *J* = 6.8 Hz, 1H), 3.58 (t, *J* = 6.8 Hz, 1H), 3.47-3.50 (m, 4H), 2.93-2.95 (m, 2H), 2.35 (s, 3H), 1.80-1.86 (m, 1H), 1.73-1.78 (m, 2H), 1.48-1.50 (m, 1H).

EXAMPLE 10: *N,N*-Dimethyl-2-(2-(4-methylpyrimidin-2-ylamino)-4,5-dihydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-6(8*H*)-yl)acetamide (Final Compound 1-17)

3-(Benzylamino)-N-methoxy-1-(4-methoxybenzyl)-N-methyl-1H-pyrazole-4-carboxamide

According to Scheme 8, Step 1: The title compound was obtained using the same procedure as described in Scheme 1, Step 5 with 3-chloro-*N*-methoxy-1-(4-methoxybenzyl)-*N*-methyl-1*H*-pyrazole-4-carboxamide (2.00 g, 6.46 mmol, synthesized as Scheme 1, Step 4) and pentylmethanamine (7.05 mL, 64.6 mmol) in

NMP (15 mL) to yield 3-(benzylamino)-*N*-methoxy-1-(4-methoxybenzyl)-*N*-methyl-1*H*-pyrazole-4-carboxamide (1.31 mmol, 500 mg, 12%).

UPLC-MS: RT = 1.04 min; MS m/z ES^+= 381.

3-(Allyl(benzyl)amino)-N-methoxy-1-(4-methoxybenzyl)-N-methyl-1H-pyrazole-4-carboxamide

According to Scheme 8, Step 2: The title compound was obtained using the same procedure as described in Scheme 1, Step 6 with 3-(benzylamino)-*N*-methoxy-1-(4-methoxybenzyl)-*N*-methyl-1*H*-pyrazole-4-carboxamide (3.00 g, 3.15 mmol), NaH (378 mg, 9.46 mmol, 60%) and 3-bromoprop-1-ene (0.53 mL 6.31 mmol) in THF/DMF (1/1, 40 mL) to yield 3-(allyl(benzyl)amino)-*N*-methoxy-1-(4-methoxybenzyl)-*N*-methyl-1*H*-pyrazole-4-carboxamide (1.28 mmol, 540 mg, 41%).

UPLC-MS: RT = 1.13 min; MS m/z ES^+= 421.

1-(3-(Allyl(benzyl)amino)-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)prop-2-en-1-one

According to Scheme 8, Step 3: The title compound was obtained using the same procedure as described in Scheme 1, Step 7 with 3-(allyl(benzyl)amino)-*N*-methoxy-1-(4-methoxybenzyl)-*N*-methyl-1*H*-pyrazole-4-carboxamide (540 mg, 1.28 mmol) and vinylmagnesium bromide (3.85 mL, 3.85 mmol) in THF (10 mL) to yield 1-(3-(allyl(benzyl)amino)-1-(4-methoxybenzyl)-1*H*-pyrazol-4-yl)prop-2-en-1-one (1.19 mmol, 460 mg, 92%).

UPLC-MS: RT = 1.26 min; MS m/z ES^+= 388.

(Z)-8-Benzyl-2-(4-methoxybenzyl)-7,8-dihydropyrazolo[3,4-b]azepin-4(2H)-one

According to Scheme 8, Step 4: The title compound was obtained using the same procedure as described in Scheme 1, Step 8 with 1-(3-(allyl(benzyl)amino)-1-(4-methoxybenzyl)-1*H*-pyrazol-4-yl)prop-2-en-1-one (460 mg, 1.19 mmol) and Grubbs catalyst 2nd generation (benzylidene[1,3-*bis*(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium, 101 mg, 0.12 mmol)

to yield (*Z*)-8-benzyl-2-(4-methoxybenzyl)-7,8-dihydropyrazolo[3,4-*b*]azepin-4(2*H*)-one (0.61 mmol, 220 mg, 52%).

UPLC-MS: RT = 1.08 min ; MS m/z ES^+=360.

2-(4-Methoxybenzyl)-5,6,7,8-tetrahydropyrazolo[3,4-b]azepin-4(2H)-one

According to Scheme 8, Step 5: The title compound was obtained using the same procedure as described in Scheme 1, Step 9 with (*Z*)-8-benzyl-2-(4-methoxybenzyl)-7,8-dihydropyrazolo[3,4-*b*]azepin-4(2*H*)-one (170 mg, 0.47 mmol), ammonium formate (298 mg, 4.73 mmol) and $Pd(OH)_2$ (13.3 mg, 95.0 µmol) to yield 2-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrazolo[3,4-*b*]azepin-4(2*H*)-one (221 µmol, 60 mg, 47%).

UPLC-MS: RT = 0.68 ; MS m/z ES^+=272.

2-(2-(4-Methoxybenzyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[3,4-b]azepin-8(2H)-yl)-N,N-dimethylacetamide

According to Scheme 8, Step 6, Method A: To a solution of 2-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrazolo[3,4-*b*]azepin-4(2*H*)-one (200 mg, 0.74 mmol) in THF (1 mL) was added 60% NaH (59.0 mg, 1.47 mmol) at 0°C and the reaction mixture was stirred at rt for 30 min. 2-Chloro-*N,N*-dimethylacetamide (91 µL, 885 µmol) was then added and the reaction mixture was stirred at reflux for 30 min. Water was added to the mixture. The aqueous layer was extracted 3 times with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel using (DCM/EtOH/NH_3, 90:9:1) (100:0 to 50:50) as eluent to yield 2-(2-(4-methoxybenzyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[3,4-*b*]azepin-8(2*H*)-yl)-*N,N*-dimethylacetamide (0.34 mmol, 122 mg, 46%).

UPLC-MS: RT = 0.73 ; MS m/z ES^+= 357.

N,N-Dimethyl-2-(2-(4-methylpyrimidin-2-ylamino)-4,5-dihydropyrazolo[3,4-*b*]thiazolo [4,5-*d*]azepin-6(8*H*)-yl)acetamide (18 µmol, 6.8 mg, 62%) was obtained as a yellow

solid following the same experimental part as described in the Scheme 1 from Steps 10 to 12, Method A.

UPLC-MS: RT = 0.67 min; MS m/z ES^+= 385;

^{1}H-NMR (300 MHz, CD_3OD): 8.4 (1H, d, 5.1Hz), 7.8 (1H, s), 6.8 (1H, d, 5.1Hz), 4.3 (2H, s), 3.5 (2H, m), 3.1 (2H, m), 3.1 (3H, s), 2.9 (3H, s), 2.5 (3H, s).

EXAMPLE 11: *N*-(5-Fluoropyrimidin-2-yl)-6-(3-methoxypropyl)-4,5,6,8-tetra hydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (Final Compound 1-33)

2-(4-Methoxybenzyl)-8-(3-methoxypropyl)-5,6,7,8-tetrahydropyrazolo[3,4-b]azepin-4 (2H)-one

According to Scheme 8, Step 6, Method C: A mixture of KO*t*Bu (310 mg, 2.76 mmol), 18-Crown-6 (731 mg, 2.76 mmol) and 2-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrazolo[3,4-*b*]azepin-4(2*H*)-one (500 mg, 1.84 mmol) in THF (9.2 mL) was stirred at rt for 15 min. Then 1-bromo-3-methoxypropane (423 mg, 2.76 mmol) was added and the reaction mixture was stirred at 50°C for 45 min. As the conversion was not complete, all the reagents were added. The solvent was evaporated under reduced pressure and the crude residue was diluted with EtOAc. The organic layer was washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel using cyclohexane/EtOAc (100:0 to 40:60) as eluent to yield the title compound (0.81 mmol, 280 mg, 44%).

UPLC-MS: RT = 0.86 min; MS m/z ES^+= 344.

N-(5-fluoropyrimidin-2-yl)-6-(3-methoxypropyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine (16 µmol, 6 mg, 5%) was obtained as a yellow solid following the same experimental part as described in the Scheme 4.

UPLC-MS: RT = 0.82 min; MS m/z ES^+= 376;

^{1}H-NMR (300 MHz, $CDCl_3$): 8.68 (2H, s), 7.88 (1H, s), 3.68-3.66 (2H, m), 3.53-3.40 (4H, m), 3.36 (3H, s), 3.11-3.08 (2H, m), 2.00-1.95 (2H, m).

EXAMPLE 12: 6-(Cyclohexylmethyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,8-tetra hydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (Final Compound 1-38)

8-(Cyclohexylmethyl)-2-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrazolo[3,4-b]azepin-4(2H)-one

According to Scheme 8, Step 6, Method D: A mixture of (bromomethyl)cyclohexane (0.31 mL, 2.21 mmol), NaH (88 mg, 2.21 mmol) and NaI (331 mg, 2.21 mmol) in DMF (1 mL) was stirred for 30 min. Then 2-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrazolo[3,4-*b*]azepin-4(2*H*)-one (300 mg, 1.11mmol) was added and the reaction mixture was stirred at 60°C for 1 h. As the conversion was not complete, 2 more equivalents of (bromomethyl)cyclohexane were added. The mixture was quenched with NH_4Cl solution, washed with brine and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel using cyclohexane/EtOAc (100:0 to 50:50) as eluent to yield the title compound (272 µmol, 100 mg, 25%).

UPLC-MS: RT = 1.17 min; MS m/z ES^+= 367.

6-(Cyclohexylmethyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine (13 µmol, 5 mg, 32%) was obtained as a yellow solid following the same experimental part as described in the Scheme 4.

UPLC-MS: RT = 1.12 min; MS m/z ES^+= 400;

^{1}H-NMR (300 MHz, DMSO-d_6): 11.81-11.66 (2H, m), 8.69 (2H, s), 7.65 (1H, s), 3.18 (2H, d), 2.99 (2H, d), 1.73-1.60 (6H, m), 1.22-1.14 (2H, m), 0.92-0.89 (2H, m).

EXAMPLE 13: *N*-(5-Fluoropyrimidin-2-yl)-6-((5-methylisoxazol-3-yl)methyl)-4,5, 6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (Final Compound 1-22)

1-(3-Chloro-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)ethanone

According to Scheme 9, Step 1: To a solution of 3-chloro-*N*-methoxy-1-(4-methoxybenzyl)-*N*-methyl-1*H*-pyrazole-4-carboxamide (25 g, 81 mmol, synthesized as

in Scheme 1) in THF (200 mL) was added methylmagnesium bromide (19.2 g, 161 mmol) and the reaction mixture was stirred at rt for 1 h. HCl 1N was added and the solution was extracted 2 times with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the title compound (75.5 mmol, 20.0 g, 94%).

UPLC-MS: RT = 0.88 min; MS m/z ES^+= 265.

1-(3-(Allylamino)-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)ethanone

According to Scheme 9, Step 2: To a solution of 1-(3-chloro-1-(4-methoxybenzyl)-1*H*-pyrazol-4-yl)ethanone (3.00 g, 11.3 mmol) in water (40 mL) was added prop-2-en-1-amine (1.94 g, 34.0 mmol) and the reaction mixture was heated in the microwave at 130°C for 45 min (70% of conversion by UPLC/MS). To make the reaction complete, 2 equivalents of allylamine were added to the mixture then the solution was heated in the microwave for 45 min. The mixture was diluted with EtOAc and water. The aqueous and organic layers were separated. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel using cyclohexane/EtOAc (100:0 to 70:30) as eluent to yield the title compound (9.81 mmol, 2.80 g, 87%).

UPLC-MS: RT = 0.91 min; MS m/z ES^+= 286.

1-(3-(Allylamino)-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)prop-2-en-1-one

According to Scheme 9, Step 3: To a mixture of 1-(3-(allylamino)-1-(4-methoxybenzyl)-1*H*-pyrazol-4-yl)ethanone (1.00 g, 3.50 mmol), formaldehyde (526 mg, 17.5 mmol) and diisopropylammonium 2,2,2-trifluoroacetate (905 mg, 4.21 mmol) in THF (40 mL) was added TFA (45 µL) and the reaction mixture was stirred at 85°C for 2 h. Then 1 equivalent of formaldehyde and 0.2 equivalent of diisopropylammonium 2,2,2-trifluoroacetate were added. The mixture was stirred at reflux for 30 min more. 1 N HCl (10 mL) was added to the mixture and then water (50 mL) and DCE (300 mL). The aqueous and organic layers were separated. The organic layer was dried over $MgSO_4$, filtered and directly used in the next step without being concentrated.

UPLC-MS: RT = 0.98 min; MS m/z ES^+= 298.

(Z)-2-(4-Methoxybenzyl)-7,8-dihydropyrazolo[3,4-b]azepin-4(2H)-one

According to Scheme 9, Step 4: The title compound was obtained using the same procedure as described in Scheme 1, Step 8 with 1-(3-(allylamino)-1-(4-methoxybenzyl)-1*H*-pyrazol-4-yl)prop-2-en-1-one (1.00 g, 3.36 mmol) and Grubbs catalyst 1st generation (277 mg, 0.34 mmol) in DCE (300 mL) to yield (*Z*)-2-(4-methoxybenzyl)-7,8-dihydropyrazolo[3,4-*b*]azepin-4(2*H*)-one (1.50 mmol, 405 mg, 45%).

UPLC-MS: RT = 0.66 min; MS m/z ES^+= 270.

2-(4-Methoxybenzyl)-5,6,7,8-tetrahydropyrazolo[3,4-b]azepin-4(2H)-one

According to Scheme 9, Step 5: The title compound was obtained using the same procedure as described in Scheme 1, Step 9 with (*Z*)-2-(4-methoxybenzyl)-7,8-dihydropyrazolo[3,4-*b*]azepin-4(2*H*)-one (1.20 g, 4.46 mmol), $Pd(OH)_2$ (63 mg, 446 µmol) and ammonium formate (2.25 g, 35.6 mmol) in MeOH (60 mL) to yield 2-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrazolo[3,4-*b*]azepin-4(2*H*)-one (3.06 mmol, 830 mg, 69%).

UPLC-MS: RT = 0.65 min; MS m/z ES^+= 272.

N-(5-fluoropyrimidin-2-yl)-6-((5-methylisoxazol-3-yl)methyl)-4,5,6,8-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (14 µmol, 5.6 mg, 18%) was obtained as a yellow solid following the same experimental part as described in the Scheme 8 Step 6 Method A and Scheme 1 Step 10 until Scheme 1 Step 12 Method B.

UPLC-MS: RT = 0.86 min; MS m/z ES^+= 399;
^{1}H-NMR (300 MHz, DMSO-d_6): 12.0 (1H, s), 11.8 (1H, s), 8.7 (2H, s), 7.7 (1H, s), 6.1 (1H, s), 4.7 (2H, s), 3.2 (2H, m), 3.0 (2H, m), 2.3 (3H, s).

EXAMPLE 14: *N*-(5-Fluoropyrimidin-2-yl)-6-(2-(methylsulfonyl)ethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (Final Compound 1-28)

8-(2-(tert-Butyldimethylsilyloxy)ethyl)-2-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrazolo [3,4-b]azepin-4(2H)-one

According to Scheme 10, Step 1: To a solution of 2-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrazolo[3,4-*b*]azepin-4(2*H*)-one (1.00 g, 3.69 mmol, synthesized as in Scheme 8, Step5) in THF (20 mL) was added potassium 2-methylpropan-2-olate (827 mg, 7.37 mmol) and (2-bromoethoxy)(tert-butyl)dimethylsilane (4.41 g, 18.4 mmol) and the reaction mixture was stirred at 80°C for 45 min. After addition of water to the reaction mixture, the aqueous layer was extracted twice with DCM. The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. A simple filtration over silica gel yielded the title compound (2.03 mmol, 872 mg, 55%).

UPLC-MS: RT = 1.30 min; MS m/z ES^+= 431.

6-(2-(tert-Butyldimethylsilyloxy)ethyl)-N-(5-fluoropyrimidin-2-yl)-8-(4-methoxybenzyl) -4,5,6,8-tetrahydropyrazolo[3,4-b]thiazolo[4,5-d]azepin-2-amine

According to Scheme 10, Step 2: The title compound was obtained using the same procedure as described in Scheme 4, Step 1 with 1-(5-fluoropyrimidin-2-yl)thiourea (301 mg, 1.75 mmol), 8-(2-(*tert*-butyldimethylsilyloxy)ethyl)-2-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrazolo[3,4-*b*]azepin-4(2*H*)-one (750 mg, 1.75 mmol) and I_2 (443 mg, 1.75 mmol) in pyridine (10 mL) to yield 6-(2-(*tert*-butyldimethylsilyloxy)ethyl)-*N*-(5-fluoropyrimidin-2-yl)-8-(4-methoxybenzyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine (0.57 mmol, 330 mg, 32%) as a yellow solid.

UPLC-MS: RT = 1.46 min; MS m/z ES^+= 582.

2-(2-(5-Fluoropyrimidin-2-ylamino)-8-(4-methoxybenzyl)-4,5-dihydropyrazolo[3,4-b] thiazolo[4,5-d]azepin-6(8H)-yl)ethanol

According to Scheme 10, Step 3: To a solution of 6-(2-(*tert*-butyldimethylsilyloxy)ethyl)-*N*-(5-fluoropyrimidin-2-yl)-8-(4-methoxybenzyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (300 mg, 0.52 mmol) in

MeOH (1 mL) was added 6M HCl (0.5 mL) and the reaction mixture was stirred at rt for 1 h. The mixture was quenched with a saturated $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc and DCM. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the title compound (0.48 mmol, 225 mg, 93 %) as a yellow solid.

2-(2-(5-Fluoropyrimidin-2-ylamino)-8-(4-methoxybenzyl)-4,5-dihydropyrazolo[3,4-b] thiazolo[4,5-d]azepin-6(8H)-yl)ethyl 4-methylbenzenesulfonate

According to Scheme 10, Step 4: To a solution of 2-(2-(5-fluoropyrimidin-2-ylamino)-8-(4-methoxybenzyl)-4,5-dihydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-6(8*H*)-yl)ethanol (200 mg, 0.43 mmol), 4-methylbenzene-1-sulfonyl chloride (163 mg, 0.86 mmol) and *N,N*-dimethylpyridin-4-amine (10.4 mg, 86 µmol) in DCM (10 mL) was added Et_3N (119 µL, 0.86 mmol) and the reaction mixture was stirred at 90°C for 1 h. The mixture was diluted with a saturated solution of NH_4Cl. The aqueous and organic layers were separated. The aqueous layer was extracted twice with DCM. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel using cyclohexane/EtOAc (40:60) as eluent to yield the title compound (0.27 mmol, 170 mg, 64%) as a beige solid.

UPLC-MS: RT = 1.15 min; MS m/z ES^+= 622.

N-(5-Fluoropyrimidin-2-yl)-8-(4-methoxybenzyl)-6-(2-(methylsulfonyl)ethyl)-4,5,6,8-tetrahydropyrazolo[3,4-b]thiazolo[4,5-d]azepin-2-amine

According to Scheme 10, Step 5, Method A: A mixture of 2-(2-(5-fluoropyrimidin-2-ylamino)-8-(4-methoxybenzyl)-4,5-dihydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-6(8*H*)-yl)ethyl 4-methylbenzenesulfonate (10 mg, 16 µmol) and sodium methane sulfinate (7 mg, 69 µmol) in THF (1 mL) and DMF (0.5 mL) was stirred at 120°C for 30 min. The reaction mixture was concentrated under reduced pressure and the crude was used in the next step without any further purification.

UPLC-MS: RT = 0.92 min; MS m/z ES^+= 530.

N-(5-Fluoropyrimidin-2-yl)-6-(2-(methylsulfonyl)ethyl)-4,5,6,8-tetrahydropyrazolo [3,4-b]thiazolo[4,5-d]azepin-2-amine

According to Scheme 10, Step 6: The title compound was obtained using the same procedure as described in Scheme 1, Step 12, Method B with *N*-(5-fluoropyrimidin-2-yl)-8-(4-methoxybenzyl)-6-(2-(methylsulfonyl)ethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine (8.5 mg, 16 μmol) in TFA (1 mL) to yield *N*-(5-fluoropyrimidin-2-yl)-6-(2-(methylsulfonyl)ethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine (5 μmol, 2 mg, 30 %) as a yellow solid.

UPLC-MS: RT = 0.72 min; MS m/z ES^+= 410;

^{1}H-NMR (300 MHz, DMSO-d_6): 11.60-11.87 (2H, m), 8.68 (2H, s), 7.69 (1H, m), 3.65 (2H, m), 3.43 (4H, m), 3.02 (2H, m).

EXAMPLE 15: *N*-(5-Fluoropyrimidin-2-yl)-6-(2-(methylamino)ethyl)-4,5,6,8-tetra hydrohyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (Final Compound 1-32)

N-(5-Fluoropyrimidin-2-yl)-8-(4-methoxybenzyl)-6-(2-(methylamino)ethyl)-4,5,6,8-tetrahydropyrazolo[3,4-b]thiazolo[4,5-d]azepin-2-amine

According to Scheme 10, Step 5, Method B: A mixture of 2-(2-(5-fluoropyrimidin-2-ylamino)-8-(4-methoxybenzyl)-4,5-dihydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-6(8*H*)-yl)ethyl 4-methylbenzenesulfonate (50 mg, 80 μmol, synthesized as the Example 12 in Scheme 10) and methanamine (0.50 mL, 4.02 mmol) in EtOH (4 mL) was stirred at 80°C for 1 h. The reaction mixture was concentrated under reduced pressure to yield the title compound as a yellow residue which was used in the next step without any further purification.

UPLC-MS: RT = 0.70 min; MS m/z ES^+= 481.

N-(5-Fluoropyrimidin-2-yl)-6-(2-(methylamino)ethyl)-4,5,6,8-tetrahydropyrazolo[3,4-b]thiazolo[4,5-d]azepin-2-amine

According to Scheme 10, Step 6: The title compound was obtained using the same procedure as described in Scheme 1, Step 12, Method B with *N*-(5-fluoropyrimidin-2-

yl)-8-(4-methoxybenzyl)-6-(2-(methylamino)ethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine in TFA (1 mL) to yield *N*-(5-fluoropyrimidin-2-yl)-6-(2-(methylamino)ethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (6 μmol, 2.1 mg, 7%) as a yellow solid.

UPLC-MS: RT = 0.57 min; MS m/z ES^+= 361;

^{1}H-NMR (300 MHz, DMSO-d_6): 8.69 (2H, s), 7.66 (1H, s), 3.32-3.37 (4H, m), 2.98-3.02 (2H, m), 2.68-2.73 (2H, m), 2.30 (3H, s).

EXAMPLE 16: 6-(Cyclopentylmethyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,8-tetra hydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (Final Compound 1-36)

N-(5-Fluoropyrimidin-2-yl)-8-(4-methoxybenzyl)-4,5,6,8-tetrahydropyrazolo[3,4-b] thiazolo[4,5-d]azepin-2-amine

According to Scheme 11, Step 1: The title compound was obtained using the same procedure as described in Scheme 4, Step 1 with 2-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrazolo[3,4-*b*]azepin-4(2*H*)-one (1.50 g, 5.53 mmol), I_2 (1.40 g, 5.53 mmol) and 1-(5-fluoropyrimidin-2-yl)thiourea (1.14 g, 6.63 mmol) in pyridine (11.1 mL) to yield *N*-(5-fluoropyrimidin-2-yl)-8-(4-methoxybenzyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (0.94 mmol, 400 mg, 17%).

UPLC-MS: RT = 0.91 min; MS m/z ES^+= 424.

N-(5-Fluoropyrimidin-2-yl)-N,8-bis(4-methoxybenzyl)-4,5,6,8-tetrahydropyrazolo[3,4-b]thiazolo[4,5-d]azepin-2-amine

According to Scheme 11, Step 2: To a solution of *N*-(5-fluoropyrimidin-2-yl)-8-(4-methoxybenzyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (300 mg, 0.71 mmol) in DMF (4 mL) at 0°C was added NaH (45.3 mg, 1.13 mmol, 60%) and the solution was stirred at 0°C for 10 min. 1-(Chloromethyl)-4-methoxybenzene (96 μL, 0.71 mmol) was added to the mixture and the solution was stirred at 0°C for 10 min and at rt for 30 min. The mixture was diluted with EtOAc and was washed with water. The organic layer was dried over $MgSO_4$, filtered and concentrated under

reduced pressure. The crude residue was purified by flash chromatography over silica gel using DCM/(DCM/EtOH/NH_3, 90:9:1) (100:0 to 85:15) as eluent to yield the title compound (0.37 mmol, 200 mg, 34%).

UPLC-MS: RT = 1.24 min; MS m/z ES^+= 544.

6-(Cyclopentylmethyl)-N-(5-fluoropyrimidin-2-yl)-N,8-bis(4-methoxybenzyl)-4,5,6,8-tetrahydropyrazolo[3,4-b]thiazolo[4,5-d]azepin-2-amine

According to Scheme 11, Step 3: The title compound was obtained using the same procedure as described in Scheme 8, Step 6, Method B, with *N*-(5-fluoropyrimidin-2-yl)-*N*,8-*bis*(4-methoxybenzyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (100 mg, 0.18 mmol), LiHMDS (346 µL, 0.37 mmol) and (iodomethyl)cyclopentane (35 µL, 276 µmol) to yield 6-(cyclopentylmethyl)-*N*-(5-fluoropyrimidin-2-yl)-*N*,8-*bis*(4-methoxybenzyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine (128 µmol, 80 mg, 69%).

UPLC-MS: RT = 1.56 min; MS m/z ES^+= 626.

6-(Cyclopentylmethyl)-N-(5-fluoropyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-b] thiazolo[4,5-d]azepin-2-amine

According to Scheme 11, Step 4: The title compound was obtained using the same procedure as described in Scheme 1, Step 12, Method B, with 6-(cyclopentylmethyl)-*N*-(5-fluoropyrimidin-2-yl)-*N*,8-*bis*(4-methoxybenzyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (80 mg, 128 µmol) in TFA (2 mL) to yield 6-(cyclopentylmethyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine (21 µmol, 8 mg, 16%).

UPLC-MS: RT = 1.08 min; MS m/z ES^+= 386;

^{1}H-NMR (300 MHz, DMSO-d_6): 11.8 (1H, s), 11.6 (1H, s), 8.7 (2H, s), 7.6 (1H, s), 3.3 (2H, m), 3.3 (2H, m), 3.0 (2H, m), 1.4-1.8 (7H, m), 1.2 (2H, m).

EXAMPLE 17: 2-(2-(5-Fluoropyrimidin-2-ylamino)-4,5-dihydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-6(8*H*)-yl)ethanol (Final Compound 1-20)

According to Scheme 12: To a solution of *N*-(5-fluoropyrimidin-2-yl)-6-(2-methoxyethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (**Final compound 1-12**, 10 mg, 28 μmol) in DCM (0.7 mL) was added BBr_3 (138 μL, 138 μmol) at 0°C and the reaction mixture was stirred at rt for 1 h. After dilution of the reaction mixture with DCM, the organic layer was washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by preparative HPLC to yield the title compound (27 μmol, 9.4 mg, 98%) as a yellow solid.

UPLC-MS: RT = 0.64 min; MS m/z ES^+= 348;
^{1}H-NMR (300 MHz, DMSO-d_6): 11.9 (1H, s), 11.6 (1H, s), 8.7 (2H, s), 7.7 (1H, s), 4.6 (1H, s), 3.6 (2H, m), 3.4 (4H, m), 3.0 (2H, m).

EXAMPLE 18: 6-Benzyl-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,7-tetrahydropyrazolo [3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (Final Compound 1-45)

8-Benzyl-2-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrazolo[3,4-b]azepin-4(2H)-one

According to Scheme 13, Step 1: A mixture of (*Z*)-8-benzyl-2-(4-methoxybenzyl)-7,8-dihydropyrazolo[3,4-*b*]azepin-4(2*H*)-one (11.9 g, 33.1 mmol) and $Pd(OH)_2$ (5.04 g, 4.30 mmol) in AcOH/EtOH (1:1, 414 mL) was stirred at rt for 2 h under 1atm of H_2. The mixture was filtered over celite, was washed with EtOH and two products were recovered: 2-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrazolo[3,4-*b*]azepin-4(2*H*)-one and 8-benzyl-2-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrazolo[3,4-*b*]azepin-4(2*H*)-one. The benzyl compound was purified by flash chromatography over silica gel using cyclohexane/EtOAc (100:0 to 80:20) as eluent to yield the title compound (1.08 mmol, 0.39 g, 3%).

UPLC-MS: RT = 1.03 min; MS m/z ES^+= 362.

6-Benzyl-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*] azepin-2-amine (5 μmol, 2 mg, 6%) was obtained following the same experimental part as described in the Scheme 4, Step 1 Scheme 1, Step 12, Method B.

UPLC-MS: RT = 1.04 min; MS m/z ES^+= 394;

^{1}H-NMR (300 MHz, DMSO-d_6): 8.69 (2H, s), 7.72 (1H, s), 7.38-7.32 (5H, m), 4.57 (2H, s), 3.26-3.22 (2H, m), 2.96-2.93 (2H, m).

EXAMPLE 19: *N*-(5-Fluoropyrimidin-2-yl)-6-(3-methoxybenzyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (Final Compound 1-60)

8-(3-Methoxy-benzyl)-2-(2-trimethylsilanyl-ethoxymethyl)-5,6,7,8-tetrahydro-2H-1,2,8-triaza-azulen-4-one

According to Scheme 14, Step 1: A solution of 2-((2-(trimethylsilyl)ethoxy)methyl)-5,6,7,8-tetrahydropyrazolo[3,4-*b*]azepin-4(2*H*)-one (200 mg, 0.71 mmol), 1-bromomethyl-3-methoxy-benzene (284 mg, 1.42 mmol) and K_2CO_3 (196 mg, 1.42 mmol) in NMP (3 mL) was stirred at 120°C for 2 h. After cooling to rt, water (15 mL) was added and the mixture was extracted with EtOAc (15 mL×3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by Prep. HPLC (PE:EtOAc, 1 :1) to give the desired product (200 mg, 70%).

MS (ESI): *m/z* 402 **$(M+H)^+$**

5-Bromo-8-(3-methoxy-benzyl)-5,6,7,8-tetrahydro-2H-1,2,8-triaza-azulen-4-one

According to Scheme 14, Step 2: A mixture of 8-(3-methoxy-benzyl)-2-(2-trimethylsilanyl-ethoxymethyl)-5,6,7,8-tetrahydro-2*H*-1,2,8-triaza-azulen-4-one (200 mg, 0.50 mmol) and trimethyl phenylammomium tribromide (188 mg, 0.50 mmol) in $CHCl_3$ (5 mL) was refluxed for 1 h. After the reaction was finished, the mixture was washed with water (10 mL). Dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (150 mg, 86%), which was used for the next step without further purification.

MS (ESI) *m/z* 350, 352 **(M+H)$^+$**

N-(5-Fluoro-pyrimidin-2-yl)-[6-(3-methoxy-benzyl)-4,5,6,7-tetrahydropyrazolo[3,4-b][1,3]thiazolo[4,5-d]azepin-2-amine

According to Scheme 14, Step 3: A mixture of 5-bromo-8-(3-methoxy-benzyl)-5,6,7,8-tetrahydro-2*H*-1,2,8-triaza-azulen-4-one (150 mg, 0.43 mmol) and (5-fluoro-pyrimidin-2-yl)-thiourea (111 mg, 0.64 mmol) in *t*-BuOH (5 mL) and acetone (1 mL) was refluxed for 18 h. After cooling to rt, the mixture was filtered and concentrated under reduced pressure to give the crude product (15 mg, 8%).

^{1}H NMR (400MHz, DMSO-d_6): δ 8.66 (s, 2H), 7.71 (s, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 6.89-6.91 (m, 2H), 6.78 (d, *J* = 8.0 Hz, 1H), 4.52 (s, 2H), 3.70 (s, 3H), 3.22 (s, 2H), 2.93 (s, 2H).

MS (ESI) *m/z* 424 **(M+H)$^+$**

EXAMPLE 20: ***N*-(5-Fluoro-pyrimidin-2-yl)-6-(piperidin-4-ylmethyl)- 4,5,6,7-tetrahydropyrazolo[3,4-*b*][1,3]thiazolo[4,5-*d*]azepin-2-amine (Final Compound 1-78)**

2-(4-Methoxybenzyl)-8-(pyridin-4-ylmethyl)-5,6,7,8-tetrahydropyrazolo[3,4-b]azepin-4(2H)-one

According to Scheme 15, Step 1: A suspension of 2-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrazolo[3,4-*b*]azepin-4(2*H*)-one (1.6 g, 6.0 mmol), 4-(chloromethyl)pyridine (2.15 g, 17.0 mmol), K_2CO_3 (2.40 g, 14.8 mmol), LiBr (1.48 g, 17 mmol) in NMP (40 mL) was stirred at 120°C for 4 h. After cooling to rt, the mixture was extracted with EtOAc (4x100 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuum. The crude product was purified by column chromatography (PE:EtOAc, 0-40%) to give the desired product (400 mg, 47%).

MS (ESI): *m/z* 363 **(M+H)$^+$.**

tert-Butyl-4-((2-(4-methoxybenzyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[3,4-b]azepin-8 (2H)-yl)methyl)piperidine-1-carboxylate

According to Scheme 15, Step 2: A solution of 2-(4-methoxybenzyl)-8-(pyridin-4-ylmethyl)-5,6,7,8-tetrahydropyrazolo[3,4-*b*]azepin-4(2*H*)-one (400 mg, 1.10 mmol), AcOH (2 mL), Boc_2O (288 mg, 1.32 mmol) and $Pd(OH)_2$ (0.5 g) in MeOH (20 mL) was stirred under H_2 atmosphere at 50°C for 10 h. After cooling to rt, the mixture was filtered and concentrated. The residue was purified by Prep. TLC to give the title product (415 mg, 80%).

MS (ESI): *m/z* 469 **$(M+H)^+$**.

tert-Butyl-4-((5-bromo-2-(4-methoxybenzyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[3,4-b] azepin-8(2H)-yl)methyl)piperidine-1-carboxylate

According to Scheme 1, Step 10: A solution of *tert*-butyl 4-((2-(4-methoxybenzyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[3,4-*b*]azepin-8(2*H*)-yl)methyl)piperidine-1-carboxylate (415 mg, 0.90 mmol), $PhNMe_3Br_3$ (375 mg, 1.00 mmol) in $CHCl_3$ (10 mL) was stirred at 90°C for 20 min. After cooling to rt, the mixture was extracted with DCM (3x20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated to give the crude product (453 mg, 92%).

MS (ESI): *m/z* 547, 549 **$(M+H)^+$**.

tert-Butyl-4-((2-(5-fluoropyrimidin-2-ylamino)-8-(4-methoxybenzyl)-4,5-dihydro pyrazolo[3,4-b]thiazolo[4,5-d]azepin-6(8H)-yl)methyl)piperidine-1-carboxylate

According to Scheme 1, Step 11: A solution of *tert*-butyl-4-((5-bromo-2-(4-methoxybenzyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[3,4-*b*]azepin-8(2*H*)-yl)methyl) piperidine-1-carboxylate (453 mg, 0.83 mmol), (5-fluoro-pyrimidin-2-yl)-thiourea (171 mg, 0.99 mmol), in *t*-BuOH (5 mL) was stirred at 100°C for 10 h. After cooling to rt, the mixture was filtered and concentrated in vacuum. The residue was purified by Prep. TLC (PE:EtOAc, 1:1) to give the title product (110 mg, 21%).

MS (ESI): *m/z* 621 **$(M+H)^+$**.

N-(5-Fluoro-pyrimidin-2-yl)-6-(piperidin-4-ylmethyl)-4,5,6,7-tetrahydropyrazolo[3,4-b][1,3]thiazolo[4,5-d]azepin-2-amine

According to Scheme 1, Step 12: A solution of *tert*-butyl 4-((2-(5-fluoropyrimidin-2-ylamino)-8-(4-methoxybenzyl)-4,5-dihydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-6(8*H*)-yl)methyl)piperidine-1-carboxylate (110 mg, 0.18 mmol) in TFA (10 mL) was stirred at 120°C for 25 min under microwave conditions. After cooling to rt, the mixture was concentrated in vacuum and the residue was then purified by Prep. HPLC to give the title product (5 mg, 7%).

MS (ESI): *m/z* 401 **(M+H)$^+$**;

^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.64 (s, 1H), 8.67 (s, 2H), 8.42 (d, 1H, *J* = 8.4 Hz), 8.12 (d, 1H, *J* = 11.6 Hz), 7.67 (s, 1H), 3.35 (s, 2H), 3.25 (d, 4H, *J* = 6.4 Hz), 2.99 (s, 2H), 2.27-2.86 (m, 2H), 1.96-1.99 (m, 1H), 1.79 (d, 2H, *J* =12.8 Hz), 1.23-1.32 (m, 2H).

EXAMPLE 21: ***N*-(6-(Fluoromethyl)pyridin-2-yl)-6-(2-methoxyethyl) -4,5,6,7-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (Final Compound 1-83)**

2-(4-Methoxybenzyl)-8-(2-methoxyethyl)-5-thiocyanato-5,6,7,8-tetrahydropyrazolo [3,4-b]azepin-4(2H)-one

According to Scheme 16, Step 1: To a solution of 5-bromo-2-(4-methoxybenzyl)-8-(2-methoxyethyl)-5,6,7,8-tetrahydropyrazolo[3,4-*b*]azepin-4(2*H*)-one (3.00 g, 7.35 mmol) in acetone (50 mL) was added KSCN (1.07 g, 11.0 mmol) at rt and the reaction mixture was stirred overnight. Water (50 mL) was added and the mixture was extracted with EtOAc (50 mL×3). The combined organic layers were washed with water and brine, and dried over Na_2SO_4, filtered and concentrated in vacuum to give the crude product (2.6 g, 93%).

MS (ESI) *m/z* 387 **(M+H)$^+$**

2-Bromo-8-(4-methoxybenzyl)-6-(2-methoxyethyl)-4,5,6,8-tetrahydropyrazolo[3,4-b] thiazolo[4,5-d]azepine

According to Scheme 16, Step 2: To a solution of 2-(4-methoxybenzyl)-8-(2-methoxyethyl)-5-thiocyanato-5,6,7,8-tetrahydropyrazolo[3,4-*b*]azepin-4(2*H*)-one (1.00 g, 2.59 mmol) in DCM (20 mL) was added AcOH (HBr) (20 mL) at rt. The mixture was stirred for 2 h at rt. Water (50 mL) was added and the mixture was extracted with EtOAc (40 mL×3). The combined organic layers were washed with water and brine, and dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product, which was purified by Prep. TLC (PE:EtOAc, 1:1) to give the title compound (105 mg, 9%).

MS (ESI) *m/z* 449, 451 **(M+H)$^+$**

N-(6-(Fluoromethyl)pyridin-2-yl)-8-(4-methoxybenzyl)-6-(2-methoxyethyl)-4,5,6,8-tetrahydropyrazolo[3,4-b]thiazolo[4,5-d]azepin-2-amine

According to Scheme 16, Step 3: A mixture of 2-bromo-8-(4-methoxybenzyl)-6-(2-methoxyethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepine (50 mg, 0.11 mmol) 6-(fluoromethyl)pyridin-2-amine (16.6 mg, 132 μmol), $Pd_2(dba)_3$ (5 mg, 55 μmol), Xantphos (6.4 mg, 11 μmol) and Cs_2CO_3 (179 mg, 0.22 mmol) in dioxane (3 mL) was stirred under N_2 atmosphere at 100°C for 2 h. After cooling to rt, the mixture was filtered and concentrated in vacuum and purified by TLC (PE:EtOAc, 1:1) to give the title product 12 mg, 18%).

MS (ESI): *m/z* 495 **(M+H)$^+$**

N-(6-(Fluoromethyl)pyridin-2-yl)-6-(2-methoxyethyl)-4,5,6,7-tetrahydropyrazolo[3,4-b]thiazolo[4,5-d]azepin-2-amine

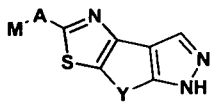
According to Scheme 16, Step 4: A solution of *N*-(6-(fluoromethyl)pyridin-2-yl)-8-(4-methoxybenzyl)-6-(2-methoxyethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine (12 mg, 24 μmol) in TFA (3 mL) was stirred at 100°C under microwave conditions for 1 h. After cooling to rt, the mixture was filtered, concentrated and purified by Prep. HPLC to give the final product (5 mg, 21%).

MS (ESI): *m/z* 375 **(M+H)$^+$;**

^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.26 (s, 1H), 7.70-7.76 (m, 2H), 7.02 (d, 1H, *J* =8.4 Hz), 6.97 (d, 1H, *J* = 7.6 Hz), 5.40 (d, 2H, *J* = 44 Hz), 3.53 (s, 4H), 3.41-3.43 (m, 2H), 3.24 (s, 3H), 2.97-2.99 (m, 2H).

The compounds in the following Table have been synthezised according to the same methods as previous Examples 1 to 21, 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.



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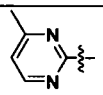
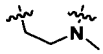
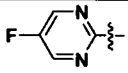
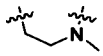
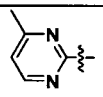
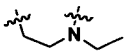
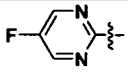
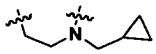
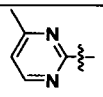
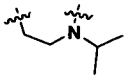
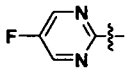
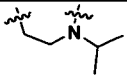
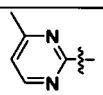
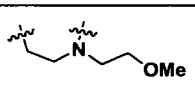
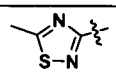
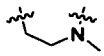
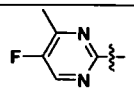
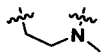
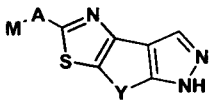
1-1*	1*		NH	
1-2	3*		NH	
1-3	1		NH	
1-4	4*		NH	
1-5	2*		NH	
1-6	4		NH	
1-7	2		NH	
1-8	2		NH	
1-9	4		NH	



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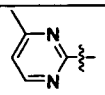
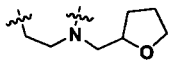
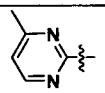
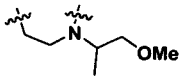
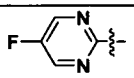
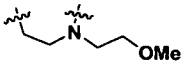
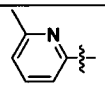
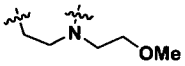
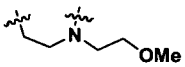
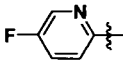
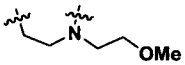
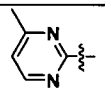
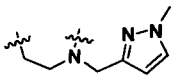
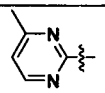
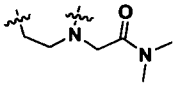
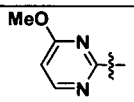
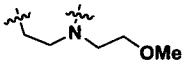
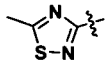
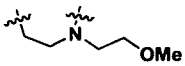
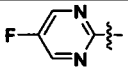
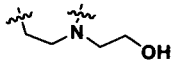
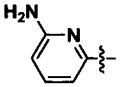
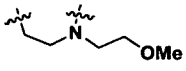
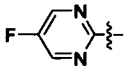
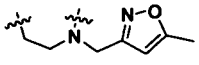
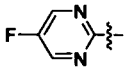
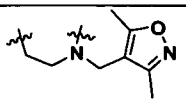
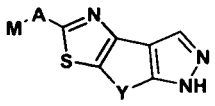
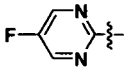
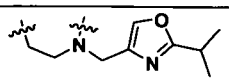
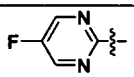
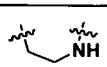
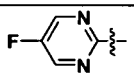
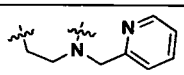
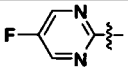
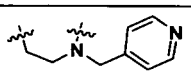
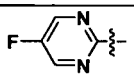
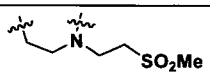
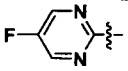
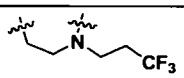
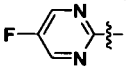
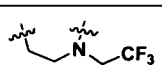
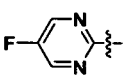
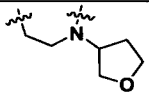
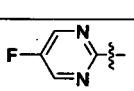
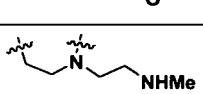
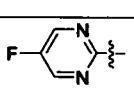
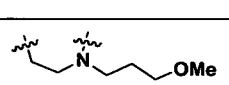
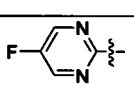
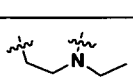
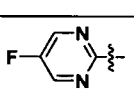
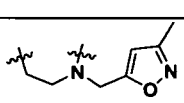
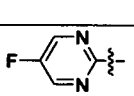
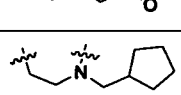
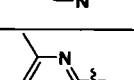
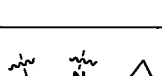
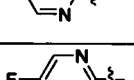
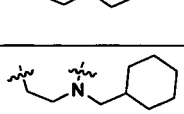
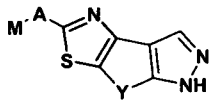
1-10	9*		NH	
1-11	2		NH	
1-12	9		NH	
1-13	5*		NH	
1-14	2		NH	
1-15	2		NH	
1-16	7*		NH	
1-17	10*		NH	
1-18	2		NH	
1-19	2		NH	
1-20	17*		NH	
1-21	2		NH	
1-22	13*		NH	
1-23	10		NH	



Co.nr.	Exp nr.	M	A	Y
1-24	10		NH	
1-25	13		NH	
1-26	6*		NH	
1-27	13		NH	
1-28	14*		NH	
1-29	8*		NH	
1-30	7		NH	
1-31	8		NH	
1-32	15*		NH	
1-33	11*		NH	
1-34	9		NH	
1-35	11		NH	
1-36	16*		NH	
1-37	8		NH	
1-38	12*		NH	



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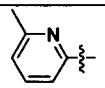
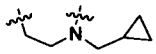
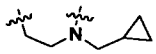
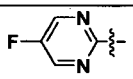
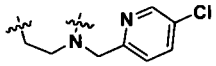
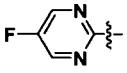
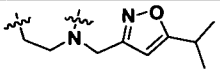
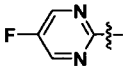
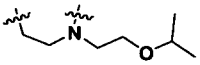
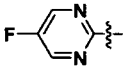
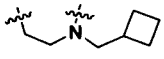
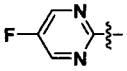
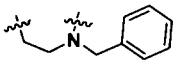
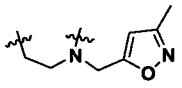
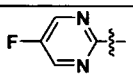
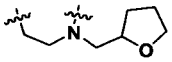
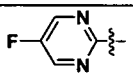
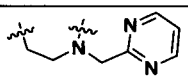
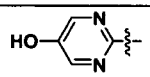
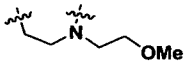
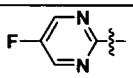
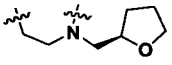
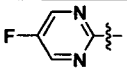
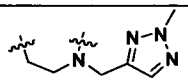
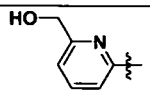
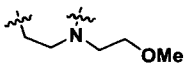
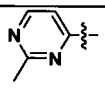
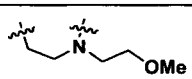
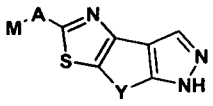
1-39	2		NH	
1-40	2		NH	
1-41	11		NH	
1-42	11		NH	
1-43	10		NH	
1-44	12		NH	
1-45	18*		NH	
1-46	19		NH	
1-48	9		NH	
1-49	9		NH	
1-50	4		NH	
1-51	9		NH	
1-52	9		NH	
1-53	2		NH	
1-54	2		NH	



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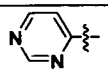
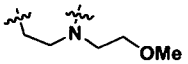
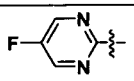
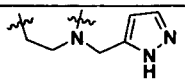
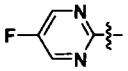
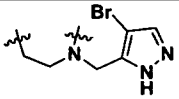
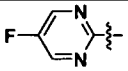
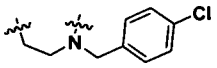
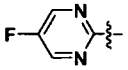
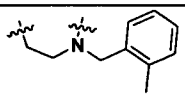
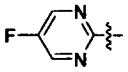
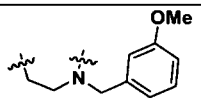
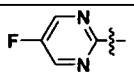
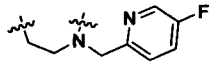
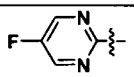
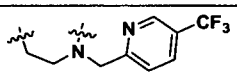
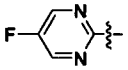
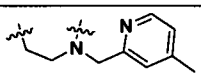
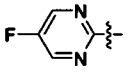
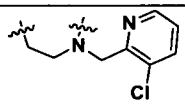
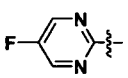
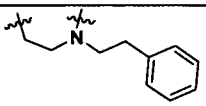
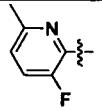
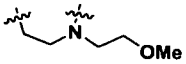
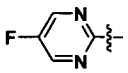
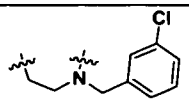
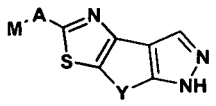
1-55	2		NH	
1-56	9		NH	
1-57	9		NH	
1-58	9		NH	
1-59	9		NH	
1-60	19*		NH	
1-61	9		NH	
1-62	9		NH	
1-63	9		NH	
1-64	9		NH	
1-65	9		NH	
1-66	5		NH	
1-67	9		NH	



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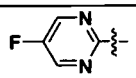
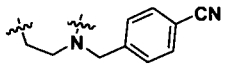
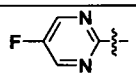
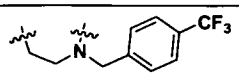
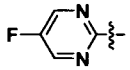
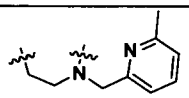
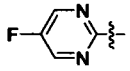
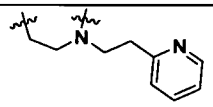
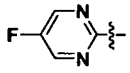
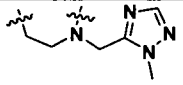
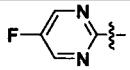
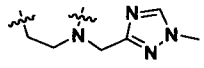
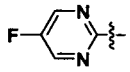
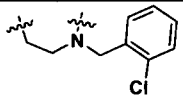
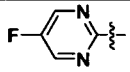
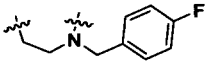
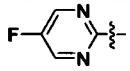
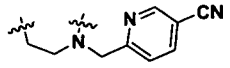
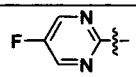
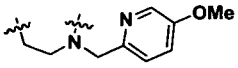
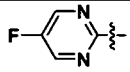
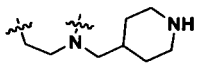
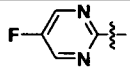
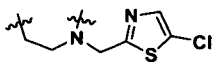
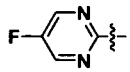
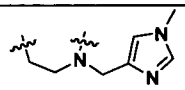
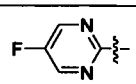
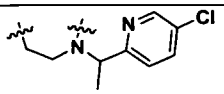
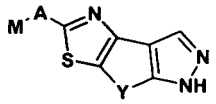
1-68	9		NH	
1-69	9		NH	
1-70	9		NH	
1-71	9		NH	
1-72	9		NH	
1-73	9		NH	
1-74	9		NH	
1-75	9		NH	
1-76	9		NH	
1-77	9		NH	
1-78	20*		NH	
1-79	9		NH	
1-80	9		NH	
1-81	9		NH	



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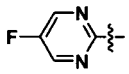
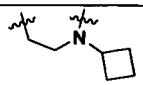
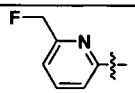
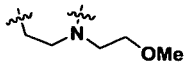
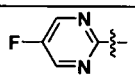
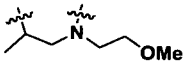
1-82	9		NH	
1-83	21*		NH	
1-84	9		NH	

UPLC-MS method:

UPLC-MS were recorded on Waters ACQUITY UPLC with the following conditions: Reversed phase HPLC was carried out on BEH-C_{18} cartridge (1.7 µm, 2.1 x 50 mm) from Waters, with a flow rate of 0.8 mL/min. The gradient conditions used are: 90 % A (water + 0.1 % of formic acid), 10% B (acetonitrile + 0.1 % of formic acid) to 100 % B at 1.3 minutes, kept till 1.6 minutes and equilibrated to initial conditions at 1.7 minutes until 2.0 minutes. Injection volume 5 µL. ES MS detector was used, acquiring both in positive and negative ionization modes.

All mass spectra were taken under electrospray ionisation (ESI) methods.

Table 2 : Physico-chemical data for some compounds (nd = not determined).

Co.Nr	M. p. (°C)	MW (theor)	[MH^+]	RT (min)
1-1	292	313.38	314	0.72
1-2	nd	317.34	318	0.72
1-3	nd	327.41	328	0.77
1-4	nd	357.41	358	0.92
1-5	247	341.43	342	0.85

Co.Nr	M. p. (°C)	MW (theor)	[MH$^+$]	RT (min)
1-6	nd	345.40	346	0.86
1-7	nd	357.43	358	0.75
1-8	291	319.41	320	0.72
1-9	nd	331.31	332	0.81
1-10	nd	383.47	384	1.69
1-11	233	371.46	372	1.69
1-12	nd	361.40	362	0.79
1-13	nd	356.45	357	0.68
1-14	203	360.41	361	0.86
1-15	218	360.41	361	0.84
1-16	nd	393.47	394	0.74
1-17	nd	384.46	385	0.67
1-18	nd	373.43	374	0.67
1-19	nd	363.46	364	0.76
1-20	nd	347.37	348	0.64
1-21	nd	357.43	358	0.54
1-22	nd	398.42	399	0.86
1-23	275	412.44	413	0.86
1-24	271	426.47	426	0.95
1-25	312	303.32	304	0.63
1-26	nd	394.43	395	0.62
1-27	nd	394.43	395	0.62
1-28	nd	409.46	410	0.72
1-29	nd	399.37	400	0.98
1-30	nd	385.07	386	nd
1-31	nd	373.41	374	0.77
1-32	nd	360.41	361	0.57
1-33	nd	375.42	376	0.82

Co.Nr	M. p. (°C)	MW (theor)	[MH$^+$]	RT (min)
1-34	306	331.37	332	0.79
1-35	280	398.42	399	0.85
1-36	nd	385.46	386	1.08
1-37	nd	353.44	354	0.87
1-38	nd	399.49	400	1.12
1-39	285	352.46	353	0.80
1-40	297	356.42	357	0.97
1-41	nd	428.87	429	0.94
1-42	nd	426.47	427	1.02
1-43	nd	389.45	391	0.95
1-44	nd	371.44	372	0.99
1-45	nd	393.44	394	1.04
1-46	nd	394.45	395	0.84
1-48	nd	387.43	388	nd
1-49	nd	395.42	396	nd
1-50	nd	359.12	360	nd
1-51	nd	387.13	388	nd
1-52	nd	398.12	399	nd
1-53	nd	372.14	373	nd
1-54	nd	357.14	358	nd
1-55	nd	343.12	344	nd
1-56	nd	383.11	384	nd
1-57	nd	461.02	462, 464	nd
1-58	nd	427.08	428, 430	nd
1-59	nd	407.13	408	nd
1-60	nd	423.13	424	nd
1-61	nd	412.10	413	nd
1-62	nd	462.10	463	nd

Co.Nr	M. p. (°C)	MW (theor)	[MH$^+$]	RT (min)
1-63	nd	408.13	409	nd
1-64	nd	428.07	429, 431	nd
1-65	nd	407.13	408	nd
1-66	nd	374.13	375	nd
1-67	nd	427.08	428, 430	nd
1-68	nd	418.11	419	nd
1-69	nd	461.10	462	nd
1-70	nd	408.13	409	nd
1-71	nd	408.13	409	nd
1-72	nd	398.12	399	nd
1-73	nd	398.12	399	nd
1-74	nd	427.08	428, 430	nd
1-75	nd	411.11	412	nd
1-76	nd	419.11	420	nd
1-77	nd	424.12	425	nd
1-78	nd	400.16	401	2.28
1-79	nd	434.03	435, 437	2.89
1-80	nd	397.12	398	nd
1-81	nd	442.09	443, 445	2.55
1-82	nd	357.12	358	2.48
1-83	nd	374.13	375	nd
1-84	nd	375.13	376	2.55

Table 3 : NMR-data

Co.Nr	NMR-data
1-1	^{1}H-NMR (300MHz, DMSO-d_6) δ: 12.0 (s, 1H), 11.3 (s, 1H), 8.4 (d, 1H), 7.6 (s, 1H), 6.95 (d, 1H), 3.3 (m, 2H), 3.05(m, 2H), 2.95(s, 3H), 2.45 (s, 3H)
1-2	^{1}H-NMR (300MHz, DMSO-d_6) δ: 11.8 (s, 1H), 8.7 (s, 2H), 7.7 (s, 1H), 3.3 (m, 2H), 3.0 (m, 2H), 2.9 (s, 3H)
1-3	^{1}H-NMR (300MHz, DMSO-d_6) δ: 11.81 (1H, s), 11.36 (1H, s), 8.42 (1H, d, 4.8Hz), 7.66 (1H, s), 6.88 (1H, d, 4.8Hz), 3.35-3.41 (2H, m), 3.27-3.30 (2H, m), 2.99-3.02 (2H, m), 2.41-2.43 (3H, m)
1-4	^{1}H-NMR (300MHz, DMSO-d_6) δ: 12.0 (s, 1H), 11.3 (s, 1H) 8.7 (s, 2H), 7.6 (s, 1H), 3.4 (m, 2H), 3.1 (m, 2H), 2.95 (m, 2H), 2.45 (s, 3H).
1-5	^{1}H-NMR (300MHz, DMSO-d_6) δ: 8.43 (1H, d, 5Hz), 7.67 (1H, s), 6.88 (1H, d, 5Hz), 3.34 (1H, m), 3.20-3.17 (2H, m), 2.99-2.95 (2H, m), 2.42 (3H, s), 1.14 (6H, d, 6.7Hz).
1-6	^{1}H-NMR (300MHz, DMSO-d_6) δ: 11.6-11.9 (2H, m), 8.69 (2H, s), 7.68 (1H, s), 4.12-4.21 (1H, m), 3.18-3.21 (2H, m), 2.95-2.99 (2H, m), 1.14 (6H, d, 7Hz)
1-7	^{1}H-NMR (300MHz, DMSO-d_6) δ: 8.38 (1H, d, 5.3Hz), 7.83 (1H, s), 6.83 (1H, d, 5.3Hz), 3.61-3.65 (2H, m), 3.56-3.59 (2H, m), 3.48-3.51 (2H, m), 3.37 (3H, s), 3.03-3.07 (2H, m), 2.48 (3H, s)
1-8	^{1}H-NMR (300MHz, DMSO-d_6) δ: 12 (1H, s), 7.81 (1H, m), 3.25-3.3 (2H, m), 3.02-3.06 (2H, m), 2.95 (3H, s), 2.75 (3H, s)
1-9	^{1}H-NMR (300MHz, DMSO-d_6) δ: 12 (1H, s), 11.5 (1H, s), 8.55 (1H, s), 7.7 (1H, s), 3.25-3.3 (2H, m), 3.02-3.06 (2H, m), 2.95 (3H, s), 2.45 (3H, s)
1-10	^{1}H-NMR (400MHz, DMSO-d_6) δ: 11.76 (s, 1H), 11.31 (s, 1H), 8.38 (d, J = 4.8 Hz, 1H), 7.26 (s, 1H), 6.83 (d, J = 4.8 Hz, 1H), 4.09 (s, 1H), 3.73 (t, J = 6.8 Hz, 1H), 3.58 (t, J = 6.8 Hz, 1H), 3.47-3.50 (m, 4H), 2.93-2.95 (m, 2H), 2.35 (s, 3H), 1.80-1.86 (m, 1H), 1.73-1.78 (m, 2H), 1.48-1.50 (m, 1H).
1-11	^{1}H-NMR (300MHz, $CDCl_3$) δ: 8.39 (1H, d, 4.8Hz), 7.93 (1H, s), 6.7 (1H, d, 5.1Hz), 4.94-4.98 (1H, m), 3.61 (2H, d, 6.3Hz), 3.43-3.48 (2H, m), 3.48 (3H, s), 3.05-3.09 (2H, m), 2.5 (3H, s), 1.31 (3H, d, 6.8Hz)
1-12	^{1}H-NMR (400MHz, DMSO-d_6) δ: 11.80 (s, 1H), 11.60 (s, 1H), 8.66 (s, 2H), 7.64 (s, 1H), 3.52 (t, 4H, J = 4.4Hz), 3.36 (t, 2H, J = 4.4Hz), 3.23 (s, 3H), 2.96 (s, 2H).
1-13	^{1}H-NMR (300MHz, $CDCl_3$) δ: 8.59 (1H, s), 8.04 (1H, s), 7.51 (1H, m), 6.81-6.74 (2H, m), 3.98 (3H, s), 3.68-3.61 (4H, m), 3.53-3.49 (2H, m), 3.07-3.04 (2H, m), 2.54 (3H, s).
1-14	^{1}H-NMR (300MHz, DMSO-d_6) δ: 11.88 (1H, s), 11.4 (1H, s), 7.81-7.85 (1H, m), 6.99 (1H, dd, 8.1Hz, 2.1Hz), 6.59 (1H, dd, 8.1Hz, 2.1Hz), 3.52-3.57 (4H, m), 3.36-3.42 (2H, m), 3.27 (3H, s), 2.99-3.02 (2H, m)
1-15	^{1}H-NMR (300MHz, DMSO-d_6) δ: 11.85 (1H, s), 11.19 (1H, s), 8.24 (1H, d, 3Hz), 7.63-7.70 (2H, m), 7.11 (1H, dd, 9.3Hz, 3.6Hz), 3.51-3.59 (4H, m), 3.37-3.41 (2H, m), 3.27 (3H, s), 2.96-3.01 (2H, m)

Co.Nr	NMR-data
1-16	^{1}H-NMR (300MHz, CD_3OD) δ: 8.4 (1H, d, 4.8Hz), 7.85 (1H, s), 7.5 (1H, d, 2.3Hz), 6.8 (1H, d, 4.8Hz), 6.2 (1H, d, 2.3Hz), 4.5 (2H, s), 3.85 (3H, s), 3.35 (2H, m), 2.95 (2H, m), 2.45 (3H, s)
1-17	^{1}H-NMR (300MHz, CD_3OD) δ: 8.4 (1H, d, 5.1Hz), 7.8 (1H, s), 6.8 (1H, d, 5.1Hz), 4.3 (2H, s), 3.5 (2H, m), 3.1 (2H, m), 3.1 (3H, s), 2.9 (3H, s), 2.5 (3H, s)
1-18	^{1}H-NMR (300MHz, DMSO-d_6) δ: 11.85 (1H, s), 11.41 (1H, s), 8.28 (1H, d, 5.4Hz), 7.67 (1H, s), 6.41 (1H, d, 5.4Hz), 4 (3H, s), 3.51-3.57 (4H, m), 3.36-3.39 (2H, m), 3.26 (3H, s), 2.98-3.01 (2H, m)
1-19	^{1}H-NMR (300MHz, DMSO-d_6) δ: 7.67 (1H, s), 3.51-3.57 (4H, m), 3.36-3.41 (2H, m), 3.26 (3H, s), 2.95-3.00 (2H, m), 2.75 (3H, s)
1-20	^{1}H-NMR (400MHz, DMSO-d_6) δ: 11.9 (1H, s), 11.6 (1H, s), 8.7 (2H, s), 7.7 (1H, s), 4.6 (1H, s), 3.6 (2H, m), 3.4 (4H, m), 3.0 (2H, m)
1-21	^{1}H-NMR (300MHz, DMSO-d_6) δ: 10.64 (1H, s), 7.62 (1H, s), 7.24 (1H, t, 7.8Hz), 6.14 (1H, d, 7.5Hz), 5.93 (1H, d, 7.8Hz), 5.82 (2H, s), 3.51-3.57 (4H, m), 3.37-3.40 (2H, m), 3.26 (3H, s), 2.93-2.97 (2H, m)
1-22	^{1}H-NMR (300MHz, DMSO-d_6) δ: 12.0 (1H, s), 11.8 (1H, s), 8.7 (2H, s), 7.7 (1H, s), 6.1 (1H, s), 4.7 (2H, s), 3.2 (2H, m), 3.0 (2H, m), 2.3 (3H, s)
1-23	^{1}H-NMR (300MHz, DMSO-d_6) δ: 8.7 (s, 2H), 7.7 (s, 1H), 4.27 (s, 2H), 3.2 (m, 2H), 2.9 (m, 2H), 2.38 (s, 3H), 2.15 (s, 3H)
1-24	^{1}H-NMR (300MHz, DMSO-d_6) δ: 8.7 (s, 2H), 7.78 (s, 1H), 7.7 (s, 1H), 4.4 (s, 2H), 3.3 (s, 2H), 3.05-2.95 (m, 3H), 1.25 (d, J = 6.6 Hz, 6H)
1-25	^{1}H-NMR (300MHz, DMSO-d_6) δ: 11.58-11.74 (m, 2H), 8.69 (s, 2H), 7.58 (s, 1H), 5.94 (s, 1H), 3.23-3.30 (m, 2H), 2.94-3.00 (m, 2H)
1-26	^{1}H-NMR (300MHz, CD_3OD) δ: 8.5 (2H, s), 8.5 (1H, m), 7.9 (1H, m), 7.8 (1H, m), 7.5 (1H, m), 7.4 (1H, m), 4.7 (2H, s), 3.4 (2H, m), 3.0 (2H, m)
1-27	^{1}H-NMR (300MHz, DMSO-d_6) δ: 8.69 (2H, s), 8.49 (2H, d, 6.4Hz), 7.71 (1H, s), 7.33 (2H, d, 6.4Hz), 4.61 (2H, s), 3.01-3.05 (2H, m), 2.71-2.73 (2H, m)
1-28	^{1}H-NMR (300MHz, DMSO-d_6) δ: 11.60-11.87 (2H, m), 8.68 (2H, s), 7.69 (1H, m), 3.65 (2H, m), 3.43 (4H, m), 3.02 (2H, m)
1-29	^{1}H-NMR (300MHz, DMSO-d_6) δ: 11.7(s, 1H), 8.7 (s, 2H), 7.7 (s, 1H), 3.5 (m, 4H), 3.4(m, 2H), 3.0 (m, 2H)
1-30	^{1}H-NMR (400MHz, DMSO-d_6) δ: 11.67 (br, 1H), 8.69 (s, 2H), 7.72 (s, 1H), 4.23-4.31 (m, 2H), 3.48 (t, 2H, J= 4.4 Hz), 3.04 (t, 2H, J= 4.4 Hz)

Co.Nr	NMR-data
1-31	^{1}H-NMR (300MHz, DMSO-d_6) δ: 11.7 (1H, s), 8.7 (2H, s), 7.7 (1H, s), 3.5-3.55 (5H, m), 3.2-3.25 (2H, m), 3.02-3.06 (2H, m), 1.6-1.7 (2H, m)
1-32	^{1}H-NMR (300MHz, DMSO-d_6) δ: 8.69 (2H, s), 7.66 (1H, s), 3.32-3.37 (4H, m), 2.98-3.02 (2H, m), 2.68-2.73 (2H, m), 2.30 (3H, s)
1-33	^{1}H-NMR (300MHz, $CDCl_3$) δ: 8.68 (2H, s), 7.88 (1H, s), 3.68-3.66 (2H, m), 3.53-3.40 (4H, m), 3.36 (3H, s), 3.11-3.08 (2H, m), 2.00-1.95 (2H, m)
1-34	^{1}H-NMR (300MHz, DMSO-d_6) δ: 11.8 (1H, s), 11.6 (1H, s), 8.6 (2H, s), 7.6 (1H, s), 3.4 (2H, q, 6.9Hz), 3.3 (2H, m), 3.0 (2H, m), 1.1 (1H, t, 6.9Hz) ^{1}H-NMR (400MHz, DMSO-d_6) δ: 11.89 (s, 1H), 11.72 (s, 1H), 8.77 (s, 2H), 7.73 (s, 1H), 3.41-3.42 (m, 2H), 3.37-3.38 (m, 2H), 3.08-3.09 (m, 2H), 1.20-1.22 (m, 3H)
1-35	^{1}H-NMR (300MHz, DMSO-d_6) δ: 12 (1H, s), 11.7 (1H, s), 8.75 (2H, s), 7.7 (1H, s), 6.2 (1H, s), 4.65 (2H, s), 3.45-3.5 (2H, m), 3.02-3.06 (2H, m), 2.2 (3H, s)
1-36	^{1}H-NMR (300MHz, DMSO-d_6) δ: 11.8 (1H, s), 11.6 (1H, s), 8.7 (2H, s), 7.6 (1H, s), 3.3 (2H, m), 3.3 (2H, m), 3.0 (2H, m), 1.4-1.8 (7H, m), 1.2 (2H, m)
1-37	^{1}H-NMR (300MHz, DMSO-d_6) δ: 11.8 (1H, s), 11.4 (1H, s), 8.4 (1H, d), 7.7 (1H, s), 6.9 (1H, d), 3.41-3.45 (2H, m), 3.2 (2H, d), 3.02-3.06 (2H, m), 2.4 (3H, s), 1.15-1.2 (1H, m), 0.45 (2H, d), 0.25 (2H, d)
1-38	^{1}H-NMR (300MHz, DMSO-d_6) δ: 11.81-11.66 (2H, m), 8.69 (2H, s), 7.65 (1H, s), 3.18 (2H, d), 2.99 (2H, d), 1.73-1.60 (6H, m), 1.22-1.14 (2H, m), 0.92-0.89 (2H, m)
1-39	^{1}H-NMR (300MHz, DMSO-d_6) δ: 11 (1H, s), 7.7 (1H, s), 7.6 (1H, dd), 6.8 (1H, d), 6.7 (1H, d), 3.41-3.45 (2H, m), 3.2 (2H, d), 3.02-3.06 (2H, m), 2.4 (3H, s), 1.15-1.2 (1H, m), 0.45 (2H, d), 0.25 (2H, d)
1-40	^{1}H-NMR (300MHz, DMSO-d_6) δ: 11.9 (1H, s), 11.4 (1H, s), 7.8-7.85 (1H, m), 7.7 (1H, s), 7 (1H, d), 6.6 (1H, d), 3.41-3.45 (2H, m), 3.2 (2H, d), 3.02-3.06 (2H, m), 1.15-1.2 (1H, m), 0.45 (2H, d), 0.25 (2H, d), 0.25 (2H, d)
1-41	^{1}H-NMR (300MHz, DMSO-d_6) δ: 11.7(s, 1H), 8.7 (s, 2H), 8.5 (s, 1H), 7.8 (m,1H) 7.7 (s, 1H), 7.4 (d,1H), 4.6 (s,2H), 3.4 (m,2H), 3.0 (m, 2H)
1-42	^{1}H-NMR (300MHz, DMSO-d_6) δ: 11.96 (1H, s), 11.68 (1H, s), 8.7 (2H, s), 7.72 (1H, s), 6.14 (1H, s), 4.55 (2H, s), 4.12 (4H, dd), 1.22 (7H, d)

Co.Nr	NMR-data
1-43	^{1}H-NMR (300MHz, DMSO-d_6) δ: 11.83 (1H, s), 11.64 (1H, s), 8.69 (2H, s), 7.67 (1H, s), 3.56-3.61 (2H, m), 3.46-3.52 (2H, m), 3.38-3.42 (2H, m), 2.96-3.01 (2H, m), 1.08 (6H, d, 6.1Hz)
1-44	^{1}H-NMR (300MHz, DMSO-d_6) δ: 11.79 (1H, s), 11.65 (1H, s), 8.69 (2H, s), 7.63 (1H, s), 3.34-3.31 (4H, m), 2.99--3.95 (2H, m), 2.73-2.72 (1H, m), 2.00-1.71 (6H, m)
1-45	^{1}H-NMR (300MHz, DMSO-d_6) δ: 8.69 (2H, s), 7.72 (1H, s), 7.38-7.32 (5H, m), 4.57 (2H, s), 3.26-3.22 (2H, m), 2.96-2.93 (2H, m)
1-46	^{1}H-NMR (300MHz, DMSO-d_6) δ: 11.93 (1H, s), 11.36 (1H, s), 8.43 (1H, s), 7.7 (1H, s), 6.88 (1H, s), 4.66 (2H, s), 3.41-3.38 (2H, m), 3.06-3.03 (2H, m), 2.42 (3H, s), 2.18 (3H, s)
1-48	^{1}H-NMR (400MHz, DMSO-d_6) δ: 8.65 (s, 2H), 7.63 (s, 1H), 4.09 (s, 1H), 3.72 (t, J = 6.4 Hz, 1H), 3.59 (t, J = 6.4 Hz, 1H), 3.47-3.51 (m, 4H), 2.93-2.95 (m, 2H), 1.80-1.87 (m, 1H), 1.73-1.80 (m, 2H), 1.46-1.48 (m, 1H)
1-49	^{1}H-NMR (400MHz, DMSO-d_6) δ: 8.70 (d, J = 4.8 Hz, 2H), 8.67 (s, 2H), 7.68 (s, 1H), 7.31 (t, J = 4.8 Hz, 1H), 4.77 (s, 2H), 3.62 (s, 2H), 3.03 (t, J = 4.0 Hz, 2H)
1-50	^{1}H-NMR (400MHz, DMSO-d_6) δ: 8.16 (s, 2H), 7.71 (s, 1H), 3.49-3.52 (m, 4H), 3.37 (t, J = 4.4 Hz, 2H), 3.22 (s, 3H), 2.94 (t, J = 4.4 Hz, 2H)
1-51	^{1}H-NMR (400MHz, DMSO-d_6) δ: 8.65 (s, 2H), 7.63 (s, 1H), 4.09 (s, 1H), 3.72 (t, J = 6.4 Hz, 1H), 3.59 (t, J = 6.4 Hz, 1H), 3.47-3.51 (m, 4H), 2.93-2.95 (m, 2H), 1.80-1.87 (m, 1H), 1.73-1.80 (m, 2H), 1.46-1.48 (m, 1H)
1-52	^{1}H-NMR (400MHz, DMSO-d_6) δ: 8.66 (s, 2H), 7.69 (s, 1H), 7.57 (s, 1H), 4.54 (s, 2H), 4.06 (s, 3H), 3.26 (t, J = 4.0 Hz, 2H), 2.96 (d, J = 4.4 Hz, 2H)
1-53	^{1}H-NMR (400MHz, DMSO-d_6) δ: 7.73 (s, 2H), 6.98 (d, J = 7.2 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 4.55 (s, 2H), 3.49-3.52 (m, 4H), 3.38 (d, J = 4.8 Hz, 2H), 3.20 (s, 3H), 2.96 (d, J = 4.8 Hz, 2H)
1-54	^{1}H-NMR (300MHz, CD_3OD) δ: 8.22 (d, 1H, J = 7.2 Hz), 7.96 (s, 1H), 6.96-7.05 (m, 1H), 3.50-3.56 (m, 6H), 3.27 (s, 3H), 3.05-3.07 (m, 2H), 2.67 (s, 3H)
1-55	^{1}H-NMR (300MHz, CD_3OD) δ: 8.97 (s, 1H), 8.37 (d, 1H, J = 6.8 Hz), 8.06 (s, 1H), 7.25 (s, 1H), 3.58-3.63 (m, 6H), 3.35 (s, 3H), 3.12 (t, 2H, J = 4.8 Hz)
1-56	^{1}H-NMR (400MHz, DMSO-d_6) δ: 8.66 (s, 2H), 7.71 (s, 1H), 7.55 (s, 1H), 6.16 (s, 1H), 4.86 (s, 2H), 3.21 (s, 2H), 2.91 (s, 2H)
1-57	^{1}H-NMR (400MHz, DMSO-d_6) δ: 8.66 (s, 2H), 7.75 (s, 1H), 7.70 (s, 1H), 4.46 (s, 2H), 3.22 (s, 2H), 2.88 (s, 2H)

Co.Nr	NMR-data
1-58	^{1}H-NMR (400MHz, DMSO-d_6) δ: 8.66 (s, 2H), 7.69 (s, 1H), 7.35 (s, 4H), 4.52 (s, 2H), 3.22-3.23 (m, 2H), 2.94-2.95 (m, 2H)
1-59	^{1}H-NMR (400MHz, DMSO-d_6) δ: 8.66 (s, 2H), 7.69 (s, 1H), 7.14-7.16 (m, 1H), 7.08-7.12 (m, 3H), 4.52 (s, 2H), 3.22-3.23 (m, 2H), 2.94-2.95 (m, 2H), 2.45 (s, 3H)
1-60	^{1}H-NMR (400MHz, DMSO-d_6) δ: 8.66 (s, 2H), 7.71 (s, 1H), 7.20 (d, J = 8.0 Hz, 1H), 6.89-6.91 (m, 2H), 6.78 (d, J = 8.0 Hz, 1H), 4.52 (s, 2H), 3.70 (s, 3H), 3.22 (s, 2H), 2.93 (s, 2H)
1-61	^{1}H-NMR (400MHz, DMSO-d_6) δ: 11.65 (s, 1H), 8.68 (s, 2H), 8.48 (d, 1H, J = 2.8 Hz), 7.61-7.69 (m, 2H), 7.39-7.43 (m, 1H), 4.64 (s, 2H), 3.46 (t, 2H, J = 4.4 Hz), 3.01 (t, 2H, J = 4.4 Hz)
1-62	^{1}H-NMR (400MHz, DMSO-d_6) δ: 8.88 (s, 1H), 8.70 (s, 2H), 8.11-8.12 (d, 1H, J = 6.8 Hz), 7.77 (s, 1H), 7.56 (d, 1H, J = 8.0 Hz), 4.77 (s, 2H), 3.56 (s, 2H), 3.08 (s, 2H)
1-63	^{1}H-NMR (400MHz, CD_3OD) δ: 8.69 (s, 2H), 8.62 (d, 2H, J = 6.0 Hz), 7.81 (s, 1H), 7.72 (s, 1H), 4.83 (s, 2H), 3.54 (t, 2H, J = 4.0 Hz), 3.16 (t, 2H, J = 4.8 Hz), 2.53 (s, 3H)
1-64	^{1}H-NMR (400MHz, DMSO-d_6) δ: 8.69 (s, 2H), 8.42 (d, 1H, J = 4.0 Hz), 7.89 (d, 1H, J = 8.0 Hz), 7.68 (s, 1H), 7.30-7.33 (m, 1H), 4.80 (s, 2H), 2.98-3.10 (m, 4H)
1-65	^{1}H-NMR (400MHz, DMSO-d_6) δ: 8.66 (s, 2H), 7.78 (s, 1H), 7.25-7.26 (m, 4H), 7.17 (d, J = 8.0 Hz, 1H), 4.52 (s, 2H), 3.70 (s, 2H), 3.22 (s, 2H), 2.93 (s, 2H)
1-66	^{1}H-NMR (400MHz, DMSO-d_6) δ: 7.78 (s, 1H), 7.45-7.50 (m, 1H), 6.75-6.77 (m, 1H), 3.51-3.54 (m, 4H), 3.40-3.41 (m, 2H), 3.24 (s, 3H), 2.97-2.99 (m, 2H), 2.41 (s, 3H)
1-67	^{1}H-NMR (400MHz, DMSO-d_6) δ: 8.68 (s, 2H), 7.71 (s, 1H), 7.41 (s, 1H), 7.27-7.34 (m, 3H), 4.56 (s, 2H), 3.28 (s, 2H), 2.96-2.98 (m, 2H)
1-68	^{1}H-NMR (400MHz, CD_3OD) δ: 8.55 (s, 2H), 8.04 (s, 1H), 7.71 (d, 2H, J = 8.0 Hz), 7.52 (d, 2H, J = 8.0 Hz), 4.71 (s, 2H), 3.46 (t, 2H, J = 6.0 Hz), 3.05 (2H, J = 2.8 Hz)
1-69	^{1}H-NMR (400MHz, DMSO-d_6) δ: 8.67 (s, 2H), 7.70 (s, 1H), 7.64 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 4.52 (s, 2H), 3.22-3.23 (m, 2H), 2.94-2.95 (m, 2H)
1-70	^{1}H-NMR (400MHz, DMSO-d_6) δ: 11.83-11.91 (m, 1H), 8.87 (s, 2H), 8.38-8.42 (m, 1H), 7.90 (s, 1H), 7.81-7.85 (m, 2H), 5.00 (s, 2H), 3.29 (s, 2H), 2.82-2.86 (m, 5H)
1-71	^{1}H-NMR (400MHz, DMSO-d_6) δ: 8.74 (d, 1H, J = 4.8 Hz), 8.66 (s, 2H), 8.32 (t, 1H, J = 7.2 Hz), 7.84 (d, 1H, J = 7.6 Hz), 7.75 (d, 1H, J = 6.4 Hz), 7.67 (s, 1H), 3.27-3.35 (m, 6H), 2.91-2.92 (m, 2H)
1-72	^{1}H-NMR (400MHz, DMSO-d_6) δ: 8.64 (s, 2H), 7.77 (s, 1H), 7.66 (s, 1H), 4.63 (s, 2H), 3.40 (s, 2H), 3.84 (s, 3H), 2.95 (s, 2H)
1-73	^{1}H-NMR (400MHz, DMSO-d_6) δ: 8.66 (s, 2H), 8.44 (s, 1H), 7.71 (s, 1H), 4.54 (s, 2H), 3.79 (s, 2H), 3.41 (s, 3H), 2.95 (s, 2H)

Co.Nr	NMR-data
1-74	^{1}H-NMR (400MHz, DMSO-d_6) δ: 8.67 (s, 2H), 7.73 (s, 1H), 7.36-7.42 (m, 2H), 7.24-7.26 (m, 2H), 4.63 (s, 2H), 3.38 (s, 2H), 3.00 (s, 2H)
1-75	^{1}H-NMR (400MHz, DMSO-d_6) δ: 11.64 (s, 1H), 8.66 (s, 2H), 7.69 (s, 1H), 7.36-7.40 (m, 2H), 7.11 (t, 2H, *J* = 8.8Hz), 4.51 (s, 2H), 3.22 (t, 2H, *J* = 4.0 Hz), 2.93 (2H, *J* = 4.0Hz)
1-76	^{1}H-NMR (400MHz, DMSO-d_6) δ: 11.65 (s, 1H), 8.92 (s, 1H), 8.66 (s, 2H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.67 (s, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 4.72 (s, 2H), 3.35-3.36 (m, 2H), 3.04-3.05 (m, 2H)
1-77	^{1}H-NMR (400MHz, DMSO-d_6) δ: 8.67 (s, 2H), 8.37-8.38 (m, 1H), 7.78-7.81 (m, 1H), 7.72 (s, 1H), 7.66-7.68 (m, 1H), 4.71 (s, 2H), 3.68 (s, 3H), 3.41-3.43 (m, 2H), 3.04-3.06 (m, 2H)
1-78	^{1}H-NMR (400MHz, DMSO-d_6) δ: 11.64 (s, 1H), 8.67 (s, 2H), 8.42 (d, 1H, *J* = 8.4 Hz), 8.12 (d, 1H, *J* = 11.6 Hz), 7.67 (s, 1H), 3.35 (s, 2H), 3.25 (d, 4H, *J* = 6.4 Hz), 2.99 (s, 2H), 2.27-2.86 (m, 2H), 1.96-1.99 (m, 1H), 1.79 (d, 2H, *J* =12.8 Hz), 1.23-1.32 (m, 2H)
1-79	^{1}H-NMR (400MHz, DMSO-d_6) δ: 12.04 (s, 1H), 11.66 (s, 1H), 8.67 (s, 2H), 7.72 (s, 1H), 7.70 (s, 1H), 4.77 (s, 2H), 3.05 (s, 4H)
1-80	^{1}H-NMR (400MHz, CD_3OD) δ: 11.65 (s, 1H), 8.91 (s, 1H), 8.67 (s, 2H), 7.71 (s, 1H),. 7.56 (s, 1H), 4.55 (s, 2H), 3.79 (s, 3H), 3.30 (d, 2H, *J* = 5.2Hz), 3.02 (d, 2H, *J* = 4.0Hz)
1-81	^{1}H-NMR (400MHz, DMSO-d_6) δ: 8.66 (s, 2H), 8.56-8.57 (m, 1H), 7.83-7.86 (m, 1H), 7.76 (s, 1H), 7.48 (d, *J* = 8.4 Hz,1H), 5.32-5.37 (m, 1H), 3.28-3.33 (m, 2H), 3.07-3.12 (m, 2H), 1.52 (d, *J* = 6.4 Hz, 3H)
1-82	^{1}H-NMR (400MHz, DMSO-d_6) δ: 11.43 (s, 1H), 8.47 (s, 2H), 7.45 (s, 1H), 2.99-3.00 (m, 2H), 2.79-2.82 (m, 2H), 1.49-1.54 (m, 1H), 1.91-1.97 (m, 2H), 0.20-0.24 (m, 2H), 0.03-0.06 (m, 2H)
1-83	^{1}H-NMR (400MHz, DMSO-d_6) δ: 11.26 (s, 1H), 7.70-7.76 (m, 2H), 7.02 (d, 1H, *J* =8.4 Hz), 6.97 (d, 1H, *J* = 7.6 Hz), 5.40 (d, 2H, *J* = 44 Hz), 3.53 (s, 4H), 3.41-3.43 (m, 2H), 3.24 (s, 3H), 2.97-2.99 (m, 2H).
1-84	^{1}H-NMR (400MHz, CD_3OD) δ: 8.52 (s, 2H), 7.90 (s, 1H), 3.60-3.66 (m, 4H), 3.44 (d, 2H, *J* = 3.6 Hz), 3.35 (s, 3H), 3.30-3.32 (m, 1H), 1.34 (d, 3H, *J* = 7.2 Hz)

PHARMACOLOGY

The compounds provided in the present invention are positive allosteric modulators of $mGluR_4$. As such, these compounds do not appear to bind to the orthosteric glutamate recognition site, and do not activate the $mGluR_4$ by themselves. Instead, the response of $mGluR_4$ to a concentration of glutamate or $mGluR_4$ agonist is increased when compounds of Formula (I) to (III) are present. Compounds of Formula (I) to (III) are expected to have their effect at $mGluR_4$ by virtue of their ability to enhance the function of the receptor.

$mGluR_4$ assay on HEK-expressing human $mGluR_4$

The compounds of the present invention are positive allosteric modulators of $mGluR_4$ receptor. Their activity was examined on recombinant human $mGluR_{4a}$ receptors by detecting changes in intracellular Ca^{2+} concentration, using the fluorescent Ca^{2+}-sensitive dye Fluo4-(AM) and a Fluorometric Imaging Plate Reader (FLIPR, Molecular Devices, Sunnyvale, CA).

Transfection and Cell culture

The cDNA encoding the human metabotropic glutamate receptor ($hmGluR_4$), (accession number NM_000841.1, NCBI Nucleotide database browser), was subcloned into an expression vector containing also the hygromycin resistance gene. In parallel, the cDNA encoding a G protein allowing redirection of the activation signal to intracellular calcium flux was subcloned into a different expression vector containing also the puromycin resistance gene. Transfection of both these vectors into HEK293 cells with PolyFect reagent (Qiagen) according to supplier's protocol, and hygromycin and puromycin treatment allowed selection of antibiotic resistant cells which had integrated stably one or more copies of the plasmids. Positive cellular clones expressing $hmGluR_4$ were identified in a functional assay measuring changes in calcium fluxes in response to glutamate or selective known $mGluR_4$ orthosteric agonists and antagonists.

HEK-293 cells expressing hmGluR$_4$ were maintained in media containing DMEM, dialyzed Fetal Calf Serum (10 %), Glutamax^{TM} (2 mM), Penicillin (100 units/mL), Streptomycin (100 µg/mL), Geneticin (100 µg/mL) and Hygromycin-B (40 µg/mL) and puromycin (1 µg/mL) at 37°C/5%CO_2.

Fluorescent cell based- Ca^{2+} mobilization assay

Human mGluR$_4$ HEK-293 cells were plated out 24 hours prior to FLIPR^{384} assay in black-walled, clear-bottomed, poly-L-ornithine-coated 384-well plates at a density of 25,000 cells/well in a glutamine/glutamate free DMEM medium containing foetal bovine serum (10 %), penicillin (100 units/mL) and streptomycin (100 µg/mL) at 37°C/5 %CO_2.

On the day of the assay, the medium was aspirated and the cells were loaded with a 3 µM solution of Fluo4-AM (LuBioScience, Lucerne, Switzerland) in 0.03 % pluronic acid. After 1 hour at 37°C/ 5% CO_2, the non incorporated dye was removed by washing cell plate with the assay buffer and the cells were left in the dark at room temperature for six hours before testing. All assays were performed in a pH 7.4 buffered-solution containing 20 mM HEPES, 143 mM NaCl, 6 mM KCl, 1 mM $MgSO_4$, 1 mM $CaCl_2$, 0.125 mM sulfapyrazone and 0.1 % glucose.

After 10 s of basal fluorescence recording, various concentrations of the compounds of the invention were added to the cells. Changes in fluorescence levels were first monitored for 180 s in order to detect any agonist activity of the compounds. Then the cells were stimulated by an EC_{25} glutamate concentration for an additional 110 s in order to measure enhancing activities of the compounds of the invention. EC_{25} glutamate concentration is the concentration giving 25% of the maximal glutamate response.

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:

$$(Y=Bottom + (Top-Bottom)/(1+10^{((LogEC_{50}-X)*Hill\ Slope)}$$

allowing the determination of EC_{50} values.

The Table 4 below represents the mean EC_{50} obtained from at least three independent experiments of selected molecules performed in duplicate.

Table 4: Activity data for selected compounds

Compound no.	Ca^{2+} Flux*	Compound no.	Ca^{2+} Flux*
1-1	+++	1-40	++
1-2	++	1-41	+++
1-3	+++	1-42	+++
1-4	+++	1-43	+++
1-5	+++	1-44	+++
1-6	+++	1-45	+++
1-7	+++	1-46	+++
1-8	+++	1-48	+++
1-9	++	1-49	+++
1-10	+++	1-50	+++
1-11	+++	1-51	+++
1-12	+++	1-52	+++
1-13	+++	1-53	+
1-14	+++	1-54	+
1-15	++	1-55	+
1-16	+++	1-56	++
1-17	++	1-57	+
1-18	+++	1-58	++
1-19	+++	1-59	+

1-20	++	**1-60**	++
1-21	+++	**1-61**	+++
1-22	+++	**1-62**	+++
1-23	+++	**1-63**	+++
1-24	+++	**1-64**	++
1-25	+++	**1-65**	++
1-26	+++	**1-66**	++
1-27	+++	**1-67**	++
1-28	+++	**1-68**	+++
1-29	++	**1-69**	++
1-30	++	**1-70**	++
1-31	+++	**1-71**	+
1-32	+	**1-77**	+++
1-33	+++	**1-78**	+
1-34	+++	**1-79**	++
1-35	+++	**1-80**	++
1-36	+++	**1-81**	+++
1-37	+++	**1-82**	+
1-38	+++	**1-83**	++
1-39	++	**1-84**	++

***Table legend:**
(+): 1 μM < EC_{50} <10 μM
(++): 100 nM < EC_{50} <1 μM
(+++): EC_{50} < 100 nM

The results shown in Table 4 demonstrate that the compounds described in the present invention are positive allosteric modulators of human $mGluR_4$ receptors. These compounds do not have activity by themselves but they rather increase the functional activity and/or maximal efficacy of glutamate or $mGluR_4$ agonist.

Haloperidol-induced catalepsy model in the rat

The haloperidol-induced catalepsy is a model of Parkinson's disease. It is used to assess potential anti-parkinsonian action of compound. In this model, haloperidol, a dopamine receptor antagonist, is administered to induce catalepsy, characterized by hypokinesia and rigidity. This state is described as an acute parkinsonian state. Anti-parkinsonian drugs show efficacy in this model by decreasing the catalepsy induced by haloperidol.

Experimental design and administration procedure:

One day before the test, Male Sprague-Dawley rats (Charles River, les Oncins, France) were placed in individual cages. The day of the experiment, rats were injected with a dopamine D2 receptor antagonist, haloperidol (1.5 mg/kg, i.p.) 30 minutes prior to oral administration of test compound (1, 3, 10 and 30 mg/kg) or vehicle. L-DOPA-benserazide (150 mg/kg) used as a positive control, was also orally administered 30 min post-haloperidol injection.

Experimental procedure - Catalepsy test:

Catalepsy was assessed 60 minutes after test compound or vehicle or MTEP treatments L-DOPA-benserazide using a grid test (e.g. 90 min post-haloperidol administration). Briefly, the rats were placed on a vertical wire grid with the head pointing toward the ceiling and all paws gripping the grid. Latency to movement of both forepaws to relocate the body was measured (in seconds) with a maximum latency "cut-off" time of 120-seconds. Brain and plasma were collected at the end of the experiment for compound exposure assessment.

Unilateral 6-OHDA lesion treatments

The effect of test compounds were assessed alone or in combination with L-DOPA in male Sprague-Dawley rats lesioned through medial forebrain bundle (Taconic).

Animals were orally administered with test compounds and then tested 55-65 min post dosing in the forelimb stepping test for akinesia and 65-70 minutes post-dosing in the cylinder test. L-DOPA (2, 6 or 20 mg/kg), used as positive control and in co-therapy were ip injected. Then forelimb akinesia and cylinder tests were carried out 30-45-minutes post-dosing. In co-therapy, rats received test compound 30 minutres prior to L-DOPA and they were tested as described above between 55 and 75 minutes post test compound dosing.

Forelimb stepping test for akinesia

Stepping movements made by the isolated ipsi- and contra-lateral forelimbs are assessed. The rat's weight is centered over the isolated limb with its head and forequarters oriented forward by the experimenter. The number of rat-initiated steps that shift weight to a new location are recorded for 30-s.

Cylinder Test

Measures spontaneous forelimb use while rats voluntarily explore a cylinder (d: 20-25cm; h: 30 cm) and scored for the number of either ipsi-lateral, contra-lateral (affected limb), or both paw contacts during exploratory movements

Preference scores are calculated for ipsi-, contra-, or both forelimb contacts during a 10-minutes interval for a minimum of 20 events. For example, a zero score (lack of asymmetry) results from equal number of events for independent ipsi- versus contra-contacts, or simultaneous contacts of both paws.

Blood samples were taken immediately after testing.

Thus, the positive allosteric modulators provided in the present invention are expected to increase the effectiveness of glutamate or $mGluR_4$ agonists at $mGluR_4$ receptor. Therefore, these positive allosteric modulators are expected to be useful for treatment of various neurological and psychiatric disorders associated with glutamate dysfunction described to be treated herein and others that can be treated by such positive allosteric modulators.

The compounds of the invention can be administered either alone, or in combination with other pharmaceutical agents effective in the treatment of conditions mentioned above.

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

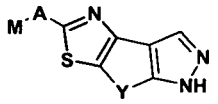
Active ingredient	5 to 1000 mg
Stearyl alcohol	3 g
Lanoline	5 g
White petroleum	15 g
Water	ad 100 g

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 having the Formula (I) wherein:



(I)

M is a an optionally substituted heteroaryl;

A is NH or O;

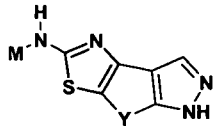
Y is selected from the group of -CO-CR^1R^2-NR^5- and -CR^1R^2-CR^3R^4-NR^5-;

R^1, R^2, R^3 and R^4 are each independently selected from the group of hydrogen, halogen, -CN, -CF_3 or an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)haloalkyl, -(C_3-C_7)cycloalkyl, aryl, heteroaryl, heterocycle, -(C_1-C_6)alkylene-aryl, -(C_1-C_6)alkylene-heteroaryl, -(C_1-C_6)alkylene-heterocycle, -O-(C_0-C_6)alkyl, -N-((C_0-C_6)alkyl)$_2$, -(C_1-C_6)alkyl-O-(C_0-C_6)alkyl, and -(C_1-C_6)alkyl-N-((C_0-C_6)alkyl)$_2$;

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; and

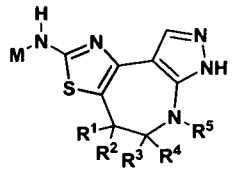
R^5 is selected from the group of hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)haloalkyl, -(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylene-(C_1-C_6)haloalkyl, -(C_1-C_6)alkylene-(C_3-C_7)halocycloalkyl, aryl, heteroaryl, heterocycle, -(C_1-C_6)alkylene-aryl, -(C_1-C_6)alkylene-heteroaryl, -(C_1-C_6)alkylene-heterocycle, -(C_2-C_6)alkyl-O-(C_0-C_6)alkyl, and -(C_2-C_6)alkyl-N-((C_0-C_6)alkyl)$_2$.

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



(II).

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



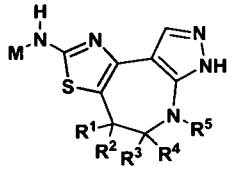
(III)

R^1, R^2, R^3 or R^4 are each independently selected from the group of hydrogen, halogen, -CN, -CF_3 or an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)haloalkyl, -(C_3-C_7)cycloalkyl, aryl, heteroaryl, heterocycle, -(C_1-C_6)alkylene-aryl, -(C_1-C_6)alkylene-heteroaryl, -(C_1-C_6)alkylene-heterocycle, -O-(C_0-C_6)alkyl, -N-((C_0-C_6)alkyl)$_2$, -(C_1-C_6)alkyl-O-(C_0-C_6)alkyl, and -(C_1-C_6)alkyl-N-((C_0-C_6)alkyl)$_2$;

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; and

R^5 is selected from the group of hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)haloalkyl, -(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylene-(C_1-C_6)haloalkyl, -(C_1-C_6)alkylene-(C_3-C_7)halocycloalkyl, aryl, heteroaryl, heterocycle, -(C_1-C_6)alkylene-aryl, -(C_1-C_6)alkylene-heteroaryl, -(C_1-C_6)alkylene-heterocycle, -(C_1-C_6)alkylene-(C_3-C_7)cycloalkyl, -(C_2-C_6)alkyl-O-(C_0-C_6)alkyl, and -(C_2-C_6)alkyl-N-((C_0-C_6)alkyl)$_2$.

4. A compound according to claim 2 having the Formula (III) wherein:



(III)

R^1, R^2, R^3 or R^4 are each independently selected from the group of hydrogen, halogen, -CN, -CF_3 or an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)haloalkyl, -(C_3-C_7)cycloalkyl, aryl, heteroaryl, heterocycle, -(C_1-C_6)alkylene-aryl, -(C_1-C_6)alkylene-heteroaryl, -(C_1-C_6)alkylene-heterocycle, -O-(C_0-C_6)alkyl, -N-((C_0-C_6)alkyl)$_2$, -(C_1-C_6)alkyl-O-(C_0-C_6)alkyl, and -(C_1-C_6)alkyl-N-((C_0-C_6)alkyl)$_2$;

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; and

R^5 is selected from the group of hydrogen or an optionally substituted radical selected from the group of -(C_1-C_6)alkyl, -(C_1-C_6)haloalkyl, -(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylene-(C_1-C_6)haloalkyl, -(C_1-C_6)alkylene-(C_3-C_7)halocycloalkyl, aryl, heteroaryl, heterocycle, -(C_1-C_6)alkylene-aryl, -(C_1-C_6)alkylene-heteroaryl, -(C_1-C_6)alkylene-heterocycle, -(C_2-C_6)alkyl-O-(C_0-C_6)alkyl, and -(C_2-C_6)alkyl-N-((C_0-C_6)alkyl)$_2$.

5. A compound according to claim 3 or claim 4 having the Formula (III) wherein:

M is an optionnally substituted pyridinyl, pyrimidinyl, thiadiazolyl, triazinyl, thiazolyl and oxadiazolyl;

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

R^5 is selected from the group of hydrogen or an optionally substituted radical selected from the group of methyl, ethyl, isopropyl, cyclobutyl, methyl-ethylene-O-methyl, tetrahydrofuranyl, methylene-amide, methylene-trifluoromethyl, methylene-cyclopropyl, methylene-cyclobutyl, methylene-cyclopentyl, methylene-cyclohexyl, methylene-phenyl, methylene-tetrahydrofuranyl, methylene-pyrazolyl, methylene-isoxazolyl, methylene-oxazolyl, methylene-triazolyl, methylene-

thiazolyl, methylene-pyrrolyl, methylene-imidazolyl, methylene-pyridinyl, methylene-pyrimidinyl, methylene-piperidinyl, ethylene-OH, ethylene-O-methyl, ethylene-O-isopropyl, ethylene-methylamine, ethylene-sulfonyl-methyl, ethylene-trifluoromethyl, ethylene-phenyl, ethylene-pyridinyl, ethylene-cyclopropyl and propylene-O-methyl.

6. A compound according to claim 3 or claim 4 having the Formula (III) wherein:

M is selected from the group of pyridinyl, pyrimidinyl, thiadiazolyl and triazinyl which can each be substituted by hydrogen, methyl, fluoro, chloro, methoxy, amino, hydroxyl, methylenehydroxy or fluoromethylene;

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

R^5 is selected from the group of hydrogen or an optionally substituted radical selected from the group of methyl, ethyl, isopropyl, cyclobutyl, methyl-ethylene-O-methyl, tetrahydrofuranyl, methylene-amide, methylene-trifluoromethyl, methylene-cyclopropyl, methylene-cyclobutyl, methylene-cyclopentyl, methylene-cyclohexyl, methylene-phenyl, methylene-tetrahydrofuranyl, methylene-pyrazolyl, methylene-isoxazolyl, methylene-oxazolyl, methylene-triazolyl, methylene-thiazolyl, methylene-pyrrolyl, methylene-imidazolyl, methylene-pyridinyl, methylene-pyrimidinyl, methylene-piperidinyl, ethylene-OH, ethylene-O-methyl, ethylene-O-isopropyl, ethylene-methylamine, ethylene-sulfonyl-methyl, ethylene-trifluoromethyl, ethylene-phenyl, ethylene-pyridinyl, ethylene-cyclopropyl and propylene-O-methyl.

7. A compound according to claims 1 to 6, which can exist as optical isomers, wherein said compound is either the racemic mixture or one or both of the individual optical isomers.

8. A compound according to claims 1 to 7, wherein said compound is selected from:

6-Methyl-*N*-(4-methylpyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-methyl-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-Ethyl-*N*-(4-methylpyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-(Cyclopropylmethyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-Isopropyl-*N*-(4-methylpyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-isopropyl-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-(2-Methoxyethyl)-*N*-(4-methylpyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine

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

9. A compound according to claims 1 to 7, wherein said compound is selected from:

6-Methyl-*N*-(5-methyl-1,2,4-thiadiazol-3-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoro-4-methylpyrimidin-2-yl)-6-methyl-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(4-Methylpyrimidin-2-yl)-6-((tetrahydrofuran-2-yl)methyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-(1-Methoxypropan-2-yl)-*N*-(4-methylpyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(2-methoxyethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-(2-Methoxyethyl)-*N*-(6-methylpyridin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(6-Fluoropyridin-2-yl)-6-(2-methoxyethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyridin-2-yl)-6-(2-methoxyethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-((1-Methyl-1*H*-pyrazol-3-yl)methyl)-*N*-(4-methylpyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N,*N*-Dimethyl-2-(2-(4-methylpyrimidin-2-ylamino)-4,5-dihydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-6(8*H*)-yl)acetamide
6-(2-Methoxyethyl)-*N*-(4-methoxypyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-(2-Methoxyethyl)-*N*-(5-methyl-1,2,4-thiadiazol-3-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
2-(2-(5-Fluoropyrimidin-2-ylamino)-4,5-dihydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-6(8*H*)-yl)ethanol

N^2-(6-(2-Methoxyethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-yl) pyridine-2,6-diamine
N-(5-Fluoropyrimidin-2-yl)-6-((5-methylisoxazol-3-yl)methyl)-4,5,6,8-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-((3,5-Dimethylisoxazol-4-yl)methyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,8-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-((2-isopropyloxazol-4-yl)methyl)-4,5,6,8-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(pyridin-2-ylmethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(pyridin-4-ylmethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(2-(methylsulfonyl)ethyl)-4,5,6,8-tetrahydropyrazolo [3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(3,3,3-trifluoropropyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(2,2,2-trifluoroethyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(tetrahydrofuran-3-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(2-(methylamino)ethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(3-methoxypropyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine
6-Ethyl-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*] azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-((3-methylisoxazol-5-yl)methyl)-4,5,6,8-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-(Cyclopentylmethyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine
6-(Cyclopropylmethyl)-*N*-(4-methylpyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine
6-(Cyclohexylmethyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine
6-(Cyclopropylmethyl)-*N*-(6-methylpyridin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine
6-(Cyclopropylmethyl)-*N*-(6-fluoropyridin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine
6-((5-Chloropyridin-2-yl)methyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,8-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-((5-isopropylisoxazol-3-yl)methyl)-4,5,6,8-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(2-isopropoxyethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine
6-(Cyclobutylmethyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine

6-Benzyl-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*] azepin-2-amine
6-((3-Methylisoxazol-5-yl)methyl)-*N*-(4-methylpyrimidin-2-yl)-4,5,6,8-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-((tetrahydrofuran-2-yl)methyl)-4,5,6,7-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(pyrimidin-2-ylmethyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
2-(6-(2-Methoxyethyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-ylamino)pyrimidin-5-ol
N-(5-Fluoropyrimidin-2-yl)-6-(((*R*)-tetrahydrofuran-2-yl)methyl)-4,5,6,7-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-((2-methyl-2*H*-1,2,3-triazol-4-yl)methyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
(6-(6-(2-Methoxyethyl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-ylamino)pyridin-2-yl)methanol
6-(2-Methoxyethyl)-*N*-(2-methylpyrimidin-4-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine
6-(2-Methoxyethyl)-*N*-(pyrimidin-4-yl)-4,5,6,8-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-((1*H*-Pyrazol-5-yl)methyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,8-tetrahydropyrazolo [3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-((4-Bromo-1*H*-pyrazol-5-yl)methyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,8-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-(4-Chlorobenzyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(2-methylbenzyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(3-methoxybenzyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine
6-((5-Fluoropyridin-2-yl)methyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,7-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-((5-(trifluoromethyl)pyridin-2-yl)methyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-((4-methylpyridin-2-yl)methyl)-4,5,6,7-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-((3-Chloropyridin-2-yl)methyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,7-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-phenethyl-4,5,6,7-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(3-Fluoro-6-methylpyridin-2-yl)-6-(2-methoxyethyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-(3-Chlorobenzyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine
4-((2-(5-Fluoropyrimidin-2-ylamino)-4,5-dihydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-6(7*H*)-yl)methyl)benzonitrile
N-(5-Fluoropyrimidin-2-yl)-6-(4-(trifluoromethyl)benzyl)-4,5,6,7-tetrahydropyrazolo [3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine

N-(5-Fluoropyrimidin-2-yl)-6-((6-methylpyridin-2-yl)methyl)-4,5,6,7-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(2-(pyridin-2-yl)ethyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine

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

10. A compound according to claims 1 to 7, wherein said compound is selected from:

N-(5-Fluoropyrimidin-2-yl)-6-((1-methyl-1*H*-1,2,4-triazol-5-yl)methyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-((1-methyl-1*H*-1,2,4-triazol-3-yl)methyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-(2-Chlorobenzyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine
6-(4-Fluorobenzyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine
6-((2-(5-Fluoropyrimidin-2-ylamino)-4,5-dihydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-6(7*H*)-yl)methyl)nicotinonitrile
N-(5-Fluoropyrimidin-2-yl)-6-((5-methoxypyridin-2-yl)methyl)-4,5,6,7-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(piperidin-4-ylmethyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*] thiazolo[4,5-*d*]azepin-2-amine
6-((5-Chlorothiazol-2-yl)methyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,7-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-((1-methyl-1*H*-imidazol-4-yl)methyl)-4,5,6,7-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-(1-(5-Chloropyridin-2-yl)ethyl)-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,7-tetrahydro pyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
6-Cyclobutyl-*N*-(5-fluoropyrimidin-2-yl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*]thiazolo [4,5-*d*]azepin-2-amine
N-(6-(Fluoromethyl)pyridin-2-yl)-6-(2-methoxyethyl)-4,5,6,7-tetrahydropyrazolo[3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine
N-(5-Fluoropyrimidin-2-yl)-6-(2-methoxyethyl)-4-methyl-4,5,6,7-tetrahydropyrazolo [3,4-*b*]thiazolo[4,5-*d*]azepin-2-amine

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

11. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claims 1 to 10 and a pharmaceutically acceptable carrier and/or excipient.

12. 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 $mGluR_4$ allosteric modulators, comprising administering to a mammal in need of such treatment or prevention, an effective amount of a compound/composition according to claims 1 to 11.

13. 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 $mGluR_4$ positive allosteric modulators, comprising administering to a mammal in need of such treatment or prevention, an effective amount of a compound/composition according to claims 1 to 11.

14. A method useful for treating or preventing central nervous system disorders selected from the group consisting of: addiction, tolerance or dependence; affective disorders, such as depression and anxiety; psychiatric disease such as psychotic disorders, attention-deficit/hyperactivity disorder and bipolar disorder; Parkinson's disease, memory impairment, Alzheimer's disease, dementia, delirium tremens, other forms of neurodegeneration, neurotoxicity, and ischemia, comprising administering to a mammalian patient in need of such treatment or prevention, an effective amount of a compound/composition according to claims 1 to 11.

15. A method useful for treating or preventing central nervous system disorders selected from the group consisting of: Parkinson's disease and movement disorders such as bradykinesia, rigidity, dystonia, drug-induced parkinsonism, dyskinesia, tardive dyskinesia, L-DOPA-induced dyskinesia, dopamine agonist-induced dyskinesia, hyperkinetic movement disorders, Gilles de la Tourette syndrome, resting tremor, action tremor, akinesia, akinetic-rigid syndrome, akathisia, athetosis, asterixis, tics, postural instability, postencephalitic parkinsonism, muscle rigidity, chorea and choreaform movements, spasticity, myoclonus, hemiballismus, progressive supranuclear palsy, restless legs

syndrome, and periodic limb movement disorder, comprising administering to a mammalian patient in need of such treatment or prevention, an effective amount of a compound/composition according to claims 1 to 11.

16. A method of claim 15 comprising administering to a mammalian patient in need of such treatment or prevention, an effective amount of a compound/composition according to claims 1 to 11 in combination with an agent selected from the group consisting of: levodopa, levodopa with a selective extracerebral decarboxylase inhibitor, carbidopa, entacapone, a COMT inhibitor, a dopamine agonist, an anticholinergic, a cholinergic agonist, a butyrophenone neuroleptic agent, a diphenylbutylpiperidine neuroleptic agent, a heterocyclic dibenzazepine neuroleptic agent, an indolone neuroleptic agent, a phenothiazine neuroleptic agent, a thioxanthene neuroleptic agent, an NMDA receptor antagonist, an MAO-B inhibitor, an $mGluR_5$ antagonist or an A_{2A} antagonist.

17. A method useful for treating or preventing central nervous system disorders selected from the group consisting of: cognitive disorders such as delirium, substance-induced persisting delirium, dementia, dementia due to HIV disease, dementia due to Huntington's disease, dementia due to Parkinson's disease, Parkinsonian-ALS demential complex, dementia of the Alzheimer's type, substance-induced persisting dementia, and mild cognitive impairment, comprising administering to a mammalian patient in need of such treatment or prevention, an effective amount of a compound/composition according to claims 1 to 11.

18. A method useful for treating affective disorders selected from the group consisting of: anxiety, agoraphobia, generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder, posttraumatic stress disorder (PTSD), social phobia, other phobias, substance-induced anxiety disorder, and acute stress disorder, comprising administering to a mammalian

patient in need of such treatment, an effective amount of a compound/composition according to claims 1 to 11.

19. 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, and substance-induced mood disorder, comprising administering to a mammalian patient in need of such treatment or prevention, an effective amount of a compound/composition according to claims 1 to 11.

20. A method useful for treating or preventing neurological disorders selected from the group consisting of: neurodegeneration, neurotoxicity or ischemia such as stroke, spinal cord injury, cerebral hypoxia, intracranial hematoma, Parkinson's disease, memory impairment, Alzheimer's disease, dementia, and delirium tremens, comprising administering to a mammalian patient in need of such treatment or prevention, an effective amount of a compound/composition according to claims 1 to 11.

21. A method useful for treating or preventing inflammatory central nervous system disorders selected from the group consisting of: multiple sclerosis forms such as benign multiple sclerosis, relapsing-remitting multiple sclerosis, secondary progressive multiple sclerosis, primary progressive multiple sclerosis, and progressive-relapsing multiple sclerosis, comprising administering to a mammalian patient in need of such treatment or prevention, an effective amount of a compound/composition according to claims 1 to 11.

22. A method useful for treating or preventing migraine, comprising administering to a mammalian patient in need of such treatment or prevention, an effective amount of a compound/composition according to claims 1 to 11.

23. A method useful for treating or preventing epilepsy and tremor, temporal lobe epilepsy, epilepsy secondary to another disease or injury such as chronic

encephalitis, traumatic brain injury, stroke or ischemia, comprising administering to a mammalian patient in need of such treatment or prevention, an effective amount of a compound/composition according to claims 1 to 11.

24. A method useful for treating or preventing inflammation and/or neurodegeneration resulting from traumatic brain injury, stroke, ischemia, spinal cord injury, cerebral hypoxia or intracranial hematoma, comprising administering to a mammalian patient in need of such treatment or prevention, an effective amount of a compound/composition according to claims 1 to 11.

25. A method useful for treating or preventing sensory, motor or cognitive symptoms resulting from traumatic brain injury, stroke, ischemia, spinal cord injury, cerebral hypoxia or intracranial hematoma, comprising administering to a mammalian patient in need of such treatment or prevention, an effective amount of a compound/composition according to claims 1 to 11.

26. A method useful for treating medulloblastomas, comprising administering to a mammalian patient in need of such treatment, an effective amount of a compound/composition according to claims 1 to 11.

27. A method useful for treating or preventing inflammatory or neuropathic pain, comprising administering to a mammalian patient in need of such treatment or prevention, an effective amount of a compound/composition according to claims 1 to 11.

28. A method useful for treating, preventing, ameliorating, controlling or reducing the risk of various metabolic disorders associated with glutamate dysfunction, comprising administering to a mammalian patient in need of such treatment, prevention, amelioration or control of the risk, an effective amount of a compound/composition according to claims 1 to 11.

29. A method useful for treating or preventing type 2 diabetes, comprising administering to a mammalian patient in need of such treatment or prevention, an effective amount of a compound/composition according to claims 1 to 11.

30. A method useful for treating or preventing diseases or disorders of the retina, retinal degeneration or macular degeneration, comprising administering to a mammalian patient in need of such treatment or prevention, an effective amount of a compound/composition according to claims 1 to 11.

31. A method useful for treating or preventing diseases or disorders of the gastrointestinal tract including gastro-esophageal reflux disease (GERD), lower esophageal sphincter diseases or disorders, diseases of gastrointestinal motility, colitis, Crohn's disease or irritable bowel syndrome (IBS), comprising administering to a mammalian patient in need of such treatment or prevention, an effective amount of a compound/composition according to claims 1 to 11.

32. Use of a compound according to claims 1 to 10 in the manufacture of a medicament for a use as defined in any of claims 12 to 31.

33. Use of a compound according to claims 1 to 10 to prepare a tracer for imaging a metabotropic glutamate receptor.

34. Use of a compound according to claims 1 to 10 as a taste agent, flavour agent, flavour enhancing agent or a food or beverage additive.

35. A compound according to claims 1 to 10 or a composition according to claim 11 for a use in a treatment or prevention as defined in any of claims 12 to 17, 19 to 25, 27 and 29 to 31.

36. A compound according to claims 1 to 10 or a composition according to claim 11 for a use as defined in claim 28.

37. A compound according to claims 1 to 10 or a composition according to claim 11 for a use in a treatment as defined in any of claims 18 and 26.