IMIDAZO[1,2-b]PYRIDAZINE DERIVATIVES AND THEIR USE AS PDE10 INHIBITORS

Field of the Invention

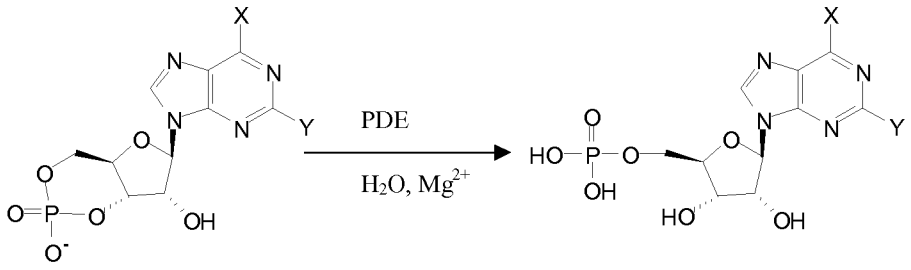
The present invention relates to novel imidazo[1,2-b]pyridazine derivatives which are inhibitors of the phosphodiesterase 10 enzyme (PDE10) and which are useful for the treatment or prevention of neurological, psychiatric and metabolic disorders in which the PDE10 enzyme is involved. The invention is also directed to pharmaceutical compositions comprising such compounds, to processes to prepare such compounds and compositions, to the use of such compounds or pharmaceutical compositions for the prevention or treatment of neurological, psychiatric and metabolic disorders and diseases.

Description of the Invention

Background of the Invention

Phosphodiesterases (PDEs) are a family of enzymes encoded by 21 genes and subdivided into 11 distinct families according to structural and functional properties. These enzymes metabolically inactivate widely occurring intracellular second messengers, 3′,5′-cyclic adenosine monophosphate (cAMP) and 3′,5′-cyclic guanosine monophosphate (cGMP). These two messengers regulate a wide variety of biological processes, including pro-inflammatory mediator production and action, ion channel function, muscle contraction, learning, differentiation, apoptosis, lipogenesis, glycogenolysis, and gluconeogenesis. They do this by activation of protein kinase A (PKA) and protein kinase G (PKG), which in turn phosphorylate a wide variety of substrates including transcription factors and ion channels that regulate innumerable physiological responses. In neurons, this includes the activation of cAMP and cGMP-dependent kinases and subsequent phosphorylation of proteins involved in acute regulation of synaptic transmission as well as in neuronal differentiation and survival. Intracellular concentrations of cAMP and cGMP are strictly regulated by the rate of biosynthesis by cyclases and by the rate of degradation by PDEs. PDEs are hydrolases that inactivate cAMP and cGMP by catalytic hydrolysis of the 3′-ester bond, forming the inactive 5′-monophosphate (Scheme A).

Scheme A



cAMP X = NH_2, Y = H
cGMP X = =O, Y = NH_2

5'-AMP/GMP

On the basis of substrate specificity, the PDE families can be divided into three groups: i) the cAMP-specific PDEs, which include PDE4, 7 and 8; ii) the cGMP-selective enzymes PDE5 and 9; and iii) the dual-substrate PDEs, PDE1, 2 and 3, as well as PDE10 and 11.

Furthermore, PDEs are expressed differentially throughout the organism, including the central nervous system. Different PDE isozymes therefore may play different physiological functions. Compounds that inhibit selectively PDE families or isozymes may display particular therapeutic activity, fewer side effects, or both.

The discovery of phosphodiesterase 10A (PDE10A) was reported in 1999. Of all the 11 known PDE families, PDE10 has the most restricted distribution with high expression only in the brain and testes.

In the brain, PDE10A mRNA and protein are highly expressed in a majority of striatal Medium Spiny Neurons (MSNs). This unique distribution of PDE10A in the brain, together with its increased pharmacological characterization, indicates a potential use of PDE10A inhibitors for treating neurological and psychiatric disorders like schizophrenia.

In the basal ganglia, MSNs constitute the major site for reception and integration of cortical glutamatergic and midbrain dopaminergic input, and form key output pathways that help discriminate and act on relevant and irrelevant cognitive and motor patterns.

MSNs are GABAergic projection neurons evenly distributed between two distinct pathways. Striatonigral MSNs (in the direct pathway) express the D_1 dopamine receptor and neuropeptides dynorphin and substance P; striatopallidal MSNs (in the indirect pathway) express the D_2 dopamine receptors and neuropeptide enkephalin. D_1 dopamine receptors are positively coupled to cAMP production, while D_2 dopamine receptors are negatively coupled to cAMP production. These pathways affect the

concentration of extracellular dopamine and modulate motor and behavioural responses.

PDE10 inhibitors and schizophrenia

Due to the predominant localisation of PDE10 in MSNs, the majority of research on PDE10 inhibitors has focused on preclinical models of psychosis.

On the basis of studies performed on knockout mice, the effects of PDE10 inhibition on striatal gene expression have been compared to the effects induced by a D_1 agonist and a D_2 antagonist.

Schizophrenia is a severe and chronic mental illness that affects approximately 1 % of the population. Clinical symptoms are apparent relatively early in life, generally emerging during adolescence or early adulthood. The symptoms of schizophrenia are usually divided into those described as positive, including hallucinations, delusions and disorganised thoughts and those referred to as negative, which include social withdrawal, diminished affection, poverty of speech and the inability to experience pleasure. In addition, schizophrenic patients suffer from cognitive deficits, such as impaired attention and memory. The aetiology of the disease is still unknown, but aberrant neurotransmitter actions have been hypothesized to underlie the symptoms of schizophrenia. The dopaminergic hypothesis is one most often considered, which proposes that hyperactivity of dopamine transmission is responsible for the positive symptoms observed in schizophrenic patients.

The efficacy of currently marketed antipsychotics correlates their ability to inhibit the D_2 dopamine receptors. Acute and chronic administration of antipsychotics such as haloperidol has characteristic effects on striatal gene expression. Inhibition of PDE10A has also been observed to produce alterations in striatal gene expression similar to those exerted by haloperidol.
Atypical antipsychotics, such as clozapine, olanzapine, risperidone and paliperidone display lower profile of extrapyramidal adverse effects and tardive dyskinesia associated with acute and long-term D_2 receptor blockade. However there is still a need to develop novel antipsychotics with lower side effects and using approaches beyond dopamine D_2 receptor blockade.

In vivo data suggest that PDE10 inhibitors can produce catalepsy, but differently to that observed with current antipsychotics, such as haloperidol, attributed to activation of both direct and indirect pathway neurons in the striatum.

PDE10 inhibitors may possess a pharmacological profile similar to that of the atypical antipsychotics, but lacking the non-target related side effects that are often observed with the currently available antipsychotics. Although EPS-like side effects are observed at relatively low doses, they are relatively mild.

Since PDE10 inhibitors can be used to raise levels of cAMP and /or cGMP within cells that express the PDE10 enzyme, for example neurons that comprise the basal ganglia, PDE10 inhibitors may be useful in treating schizophrenia and additionally, a variety of conditions involving the basal ganglia, such as the conditions described herein, for example, obesity, non-insulin dependent diabetes, bipolar disorder, obsessive compulsive disorder and pain.

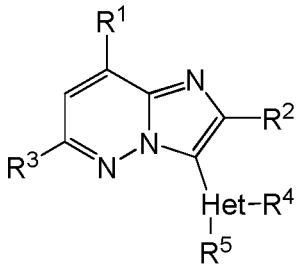
WO 2004/087710 (Pharmacia and Upjohn Company) discloses *N*-(1-ethylpropyl)-7-(6-methoxy-2-methyl-3-pyridinyl)-2,6-dimethyl-pyrrolo[1,2-*b*]pyridazin-4-amine and 7-(6-methoxy-2-methyl-3-pyridinyl)-2,6-dimethyl-*N*-(1-methylpropyl)-pyrrolo[1,2-*b*]pyridazin-4-amine as CRF receptor antagonists, WO 2006/102194 (Eli Lilly and Company) discloses imidazo[1,2-b]pyridazines bearing a 5-membered aromatic ring at the 3 position and a linear alkyl substituent at the 8-position as CRF1 receptor antagonists. The CRF receptor has been validated as a possible target for depression, anxiety, cerebrovascular disorders, irritable bowel syndrome and congestive heart failure, but not for schizophrenia.

There is still a great need for antipsychotic therapies with pharmacological profile similar to that of the atypical antipsychotics, with low extrapyramidal symptom liability.

It is the object of the present invention to provide novel compounds that are PDE10 inhibitors. The present compounds are centrally active, potent compounds which display efficacy in preclinical behavior challenge models in which known clinical useful antipsychotics display similar positive responses, such as in the reversal of apomorphine-induced stereotypy and phencyclidine (PCP)-induced hyperlocomotion in rodents. Additionally, representative compounds reverse the hypolocomotion effects exerted by SCH23390, a D1 receptor antagonist. Thus, the present compounds may act as dopamine modulating agents, inhibiting states of dopaminergic (D_2) hyperactivity and reversing states of dopaminergic (D_2) hypoactivity.

Description of the Invention

The present invention relates to compounds having PDE10 inhibitory activity, said compounds having the Formula (I)



(I)

and the stereoisomeric forms thereof, wherein

R^1 is pyridinyl; pyridinyl optionally substituted with halogen, C_{1-4}alkyl, trifluoromethyl or C_{1-4}alkyloxy; tetrahydropyranyl; or NR^6R^7;

R^2 is hydrogen, C_{1-4}alkyl, trifluoromethyl, C_{3-8}cycloalkyl, or C_{1-4}alkyloxy;

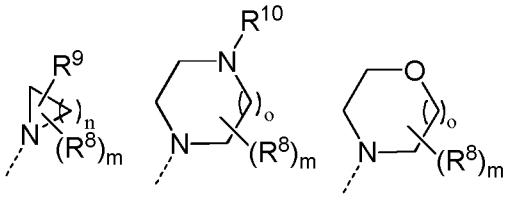
R^3 is hydrogen, chloro, C_{1-4}alkyl, trifluoromethyl, or C_{3-8}cycloalkyl;

Het is a 5- or 6- membered heterocyclic ring selected from the group consisting of pyridinyl, pyrimidinyl, pyridazinyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isothiazolyl, isoxazolyl, oxadiazolyl and triazolyl;

R^4 is hydrogen, C_{1-4}alkyl, trifluoromethylC_{0-4}alkyl, hydroxyC_{1-4}alkyl, difluorocyclopropylmethyl, cyclopropyldifluoroethyl, C_{3-8}cycloalkyl, C_{1-4}alkyloxyC_{1-5}alkyl, C_{1-4}alkyloxy, trifluoromethylC_{0-4}alkyloxy, C_{3-8}cycloalkylC_{1-4}alkyloxy, C_{3-8}cycloalkylC_{1-4}alkyl, C_{1-6}alkyloxyC_{1-4}alkyloxy, tetrahydropyranyl, pyridinylmethyl, $NR^{6a}R^{7a}C_{1-4}$alkyl or $NR^{6a}R^{7a}$;

R^5 is hydrogen or C_{1-4}alkyl;

R^6, R^{6a}, R^7 and R^{7a} are each independently hydrogen, or C_{1-4}alkyl, or taken together with N can be a radical of Formula (a), (b) or (c)



(a) **(b)** **(c) ;**

wherein

each R^8, if present, independently of one another is C_{1-4}alkyl ;

R^9 is hydrogen or C_{1-4}alkyloxy ;
R^{10} is hydrogen or C_{1-4}alkyl;
m is 0, 1, 2, 3, 4 or 5;
n is 2, 3, 4, 5 or 6;
o is 1 or 2 ;
and the pharmaceutically acceptable salts and the solvates thereof.

The present invention also relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I) and a pharmaceutically acceptable carrier or excipient.

Additionally, the invention relates to a compound of Formula (I) for use as a medicament.

The invention also relates to the use of a compound according to Formula (I) or a pharmaceutical composition according to the invention for the manufacture of a medicament for treating or preventing neurological, psychiatric or metabolic disorders and diseases.

Additionally, the invention relates to the use of a compound of Formula (I) in combination with an additional pharmaceutical agent for the manufacture of a medicament for treating or preventing neurological, psychiatric or metabolic disorders and diseases.

Furthermore, the invention relates to a process for preparing a pharmaceutical composition according to the invention, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound of Formula (I).

The invention also relates to a product comprising a compound of Formula (I) and an additional pharmaceutical agent, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of neurological, psychiatric or metabolic disorders and diseases.

Detailed description of the Invention

The Chemical names of the compounds of the present invention were generated according to the nomenclature rules agreed upon by the Chemical Abstracts Service

(CAS) using Advanced Chemical Development, Inc., software (ACD/Name product version 10.01; Build 15494, 1 Dec 2006). In case of tautomeric forms, the name of the depicted tautomeric form of the structure was generated. However it should be clear that the other non-depicted tautomeric form is also included within the scope of the present invention.

Definitions

The term "halogen" or "halo" as used herein alone or as part of another group refers to fluoro, chloro, bromo or iodo, with fluoro or chloro being preferred.

The term "C_{0-4}alkyl", "C_{1-4}alkyl" or"C_{1-5}alkyl" as employed herein alone or as part of another group, unless otherwise stated, refers to a saturated straight or branched hydrocarbon radical, having unless otherwise stated, from 0 to 4, 1 to 4 or 1 to 5 carbon atoms, which is attached to the rest of the molecule by a single bond, such as methyl, ethyl, propyl, butyl, 1-pentyl, 1-methylethyl, 1,1-dimethylethyl, 2-methylpropyl, and 3-methylbutyl.

The term "C_{3-8}cycloalkyl" as employed herein alone or as part of another group unless otherwise stated, is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

The term "subject" as used herein, refers to an animal, preferably a mammal (e.g. cat, dog, primate or human), more preferably a human, who is or has been the object of treatment, observation or experiment.

The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation or reversal of the symptoms of the disease or disorder being treated.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

As used herein, the term "treatment" is intended to refer to all processes, wherein there may be a slowing, interrupting, arresting or stopping of the progression of a disease, but does not necessarily indicate a total elimination of all symptoms.

Unless otherwise stated, heterocyclic substituents in R^1 such as tetrahydropyranyl and pyridinyl may be attached to the remainder of the molecule of formula (I) through any available ring carbon atom. Thus, for example, when Het is pyridinyl, it may be pyridin-2-yl, pyridin-3-yl or pyridin-4-yl, unless otherwise

specified.

Substituents covered by the term Het may be attached to the remainder of the molecule of formula (I) through any available ring carbon or heteroatom as appropriate, if not otherwise specified. Het as used herein, is preferably a 5- or 6- aromatic membered heterocyclic ring preferably bound to the imidazo[1,2-b]pyridazine ring system through an available carbon atom of the ring. When Het is pyridine and R^5 is methyl, the R^5 substituent is placed in Het preferably in meta- or para-position relative to the position of attachment to the imidazo[1,2-b]pyridazine core.

In one embodiment, the invention relates to a compound according to Formula (I) or a stereochemically isomeric form thereof, wherein

R^1 is selected from pyridinyl; pyridinyl optionally substituted with halogen, C_{1-4}alkyl, trifluoromethyl or C_{1-4}alkyloxy; tetrahydropyranyl; and NR^6R^7; wherein R^6 and R^7 taken together with the nitrogen can be a radical of Formula (a), (b) or (c) as previously defined;

R^2 is selected from hydrogen, methyl, ethyl, cyclopropyl, isopropyl, methoxy and trifluoromethyl ;

R^3 is selected from hydrogen, chloro, methyl, trifluoromethyl and cyclopropyl ;

Het is selected from the group consisting of pyridinyl, pyrimidinyl, pyridazinyl, oxazolyl, thiazolyl, pyrazolyl, isothiazolyl, isoxazolyl, oxadiazolyl and triazolyland R^4 – R^{10}, m, n and o are as previously defined ;

or a pharmaceutically acceptable salt or a solvate thereof.

In a more preferred embodiment, the invention relates to a compound according to Formula (I) or a stereochemically isomeric form thereof, wherein

R^1 is selected from pyridinyl which may be optionally substituted with halogen, C_{1-4}alkyl, trifluoromethyl or C_{1-4}alkyloxy; morpholinyl; and NR^6R^7; wherein R^6 and R^7 taken together with the nitrogen can be a radical of Formula (a) or (c) wherein n is 3 and o is 1;

Het is selected from pyridinyl and pyrazolyl;

R^4 is hydrogen, C_{1-4}alkyl, trifluoromethylC_{0-4}alkyl, hydroxyC_{1-4}alkyl, difluorocyclopropylmethyl, cyclopropyldifluoroethyl, C_{3-8}cycloalkyl, C_{1-4}alkyloxyC_{1-5}alkyl, C_{1-4}alkyloxy, trifluoromethylC_{0-4}alkyloxy, C_{3-8}cycloalkylC_{1-4}alkyloxy, C_{1-6}alkyloxyC_{1-4}alkyloxy, tetrahydropyranyl, pyridinylmethyl, $NR^{6a}R^{7a}C_{1-4}$alkyl or $NR^{6a}R^{7a}$;

wherein R^6, R^{6a}, R^7 and R^{7a} are each independently hydrogen or C_{1-4}alkyl, or taken together with the nitrogen can be a radical of formula (a), (b) or (c), wherein n is 3, R^9 is hydrogen or C_{1-4}alkyloxy, m is 0, o is 1 and R^{10} is hydrogen;

and the remaining variables R^2-R^5 are as previously defined;

or a pharmaceutically acceptable salt or a solvate thereof.

In another preferred embodiment, the invention relates to a compound according to Formula (I) or a stereochemically isomeric form thereof, wherein

R^1 is selected from pyridinyl, morpholinyl and pyrrolidinyl;

R^4 is selected from hydrogen ; methyl ; ethyl ; isopropyl ; isobutyl ; trifluoromethyl ; 2,2,2-trifluoroethyl ; 2-hydroxy-2-methylpropyl ; (2,2-difluorocyclopropyl)methyl ; 2,2-difluoro-2-cyclopropylethyl ; cyclopropyl ; 2-methoxyethyl ; 2-methoxypropyl ; (2*S*)-2-methoxypropyl; 2-isopropoxyethyl ; 2-ethoxyethyl ; ethoxymethyl ; 1-ethoxy-1-methylethyl ; 1-methoxy-1-methylethyl ; 2-methoxy-1,1-dimethylethyl ; 3-methoxy-3-methylbutyl ; 3-methoxypropyl ; 2-methoxy-2-methyl-propyl ; isopropoxy ; 2,2,2-trifluoroethoxy ; cyclopropylmethoxy ; 2-methoxyethoxy ; 2-methoxy-2-methyl-propoxy ; tetrahydro-*2H*-pyran-4-yl ; (pyridin-3-yl)methyl ; 2-(pyrrolidin-1-yl)ethyl ; isopropylamino ; morpholin-4-yl ; pyrrolidin-1-yl ; piperazin-1-yl ; (3*R*)-3-methoxypyrrolidin-1-yl ; and (3*S*)-3-methoxypyrrolidin-1-yl ;

R^5 is hydrogen or methyl ;

and R^2, R^3 and Het are as previously defined;

or a pharmaceutically acceptable salt or a solvate thereof.

In yet another preferred embodiment, the invention relates to a compound according to Formula (I) or a stereochemically isomeric form thereof wherein

R^1 is selected from morpholinyl and pyridinyl ;

R^2 is selected from hydrogen, methyl, ethyl, methoxy, and cyclopropyl ;

R^3 is selected from hydrogen, methyl, and cyclopropyl ;

Het is pyridinyl or pyrazolyl ;

R^4 is selected from ethyl; isopropyl; isobutyl; 2,2,2-trifluoroethyl; 2-hydroxy-2-methylpropyl; 2,2-difluoro-2-cyclopropylethyl; cyclopropyl; 2-methoxyethyl; (2*S*)-2-methoxypropyl; 2-ethoxyethyl; ethoxymethyl; 1-ethoxy-1-methylethyl; 1-methoxy-1-methylethyl; 2-methoxy-1,1-dimethylethyl; 3-methoxy-3-methylbutyl; 3-methoxypropyl; 2-methoxy-2-methyl-propyl; 2-methoxyethoxy; 2-methoxy-2-methyl-propoxy; tetrahydro-*2H*-pyran-4-yl; morpholin-4-yl; piperazin-1-yl; and (3*R*)-3-methoxypyrrolidin-1-yl;

and R^5 is hydrogen or methyl ;
or a pharmaceutically acceptable salt or a solvate thereof.

In yet another preferred embodiment, the invention relates to a compound according to Formula (I) or a stereochemically isomeric form thereof wherein
R^1 is selected from morpholinyl and pyridinyl ;
R^2 is selected from hydrogen, methyl, methoxy, and cyclopropyl ;
R^3 is selected from hydrogen, methyl, and cyclopropyl ;
Het is pyridinyl or pyrazolyl ;
R^4 is selected from ethyl; isopropyl; isobutyl; 2,2,2-trifluoroethyl; 2-hydroxy-2-methylpropyl; 2,2-difluoro-2-cyclopropylethyl; cyclopropyl; 2-methoxyethyl; (2*S*)-2-methoxypropyl; 2-ethoxyethyl; ethoxymethyl; 1-ethoxy-1-methylethyl; 1-methoxy-1-methylethyl; 2-methoxy-1,1-dimethylethyl; 3-methoxy-3-methylbutyl; 3-methoxypropyl; 2-methoxy-2-methyl-propyl; 2-methoxyethoxy; 2-methoxy-2-methyl-propoxy; tetrahydro-*2H*-pyran-4-yl; morpholin-4-yl; piperazin-1-yl; and (3*R*)-3-methoxypyrrolidin-1-yl;
and R^5 is hydrogen or methyl ;
or a pharmaceutically acceptable salt or a solvate thereof.

In yet another preferred embodiment, the invention relates to a compound according to Formula (I) or a stereochemically isomeric form thereof wherein
R^1 is selected from morpholinyl and pyridinyl ;
R^2 is selected from hydrogen, methyl, methoxy, and cyclopropyl ;
R^3 is selected from hydrogen, methyl, and cyclopropyl ;
Het is pyridinyl or pyrazolyl ;
R^4 is selected from 2-methoxyethyl; 3-methoxypropyl ; 2-methoxy-2-methylpropyl ; 2-methoxy-1,1-dimethylethyl ; 1-ethoxy-1-methylethyl ; 1-methoxy-1-methylethyl ; 2-methoxyethoxy ; ethoxymethyl ; 2-methoxy-2-methylpropoxy ; morpholin-4-yl ; 2-ethoxyethyl ; tetrahydro-*2H*-pyran-4-yl ; ethyl ; 3-methoxy-3-methylbutyl ; piperazin-1-yl ; isopropyl ; cyclopropyl ; (3*R*)-3-methoxypyrrolidin-1-yl ; and isobutyl ;
and R^5 is hydrogen or methyl ;
or a pharmaceutically acceptable salt or a solvate thereof.

More preferably, the invention relates to a compound according to Formula (I) or a stereochemically isomeric form thereof wherein
R^1 is selected from morpholin-4-yl, pyridin-3-yl and pyridin-4-yl ;

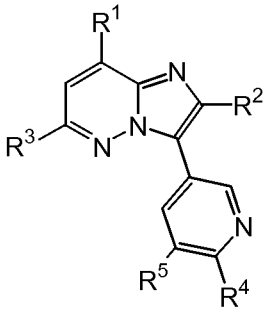
Het is selected from pyridin-3-yl, pyridin-4-yl and *1H*-pyrazol-4-yl ;
and R^2-R^5 are as previously defined ;
or a pharmaceutically acceptable salt or a solvate thereof.

In a yet a more preferred embodiment, the invention relates to a compound according to Formula (I), or a stereochemically isomeric form thereof, wherein
R^1 is morpholin-4-yl ;
Het is pyridin-3-yl or pyridin-4-yl ;
and R^2-R^5 are as previously defined ;
or a pharmaceutically acceptable salt or a solvate thereof.

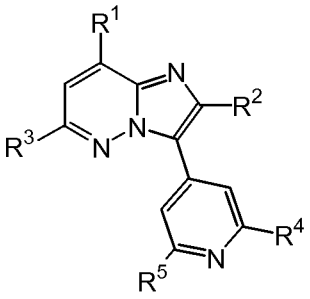
In the most preferred embodiment, the invention relates to a compound according to Formula (I) wherein
R^1 is morpholin-4-yl ;
R^2 is methyl ;
R^3 is hydrogen ;
Het is pyridin-3-yl ;
R^4 is 2-methoxyethyl ; and
R^5 is hydrogen ;
or a pharmaceutically acceptable salt or a solvate thereof.

An additional embodiment refers to compounds according to Formula (I), wherein R^3 is hydrogen and the rest of variables are as previously defined, and the stereochemically isomeric forms thereof and the pharmaceutically acceptable salts and solvates thereof.

In an additional embodiment, the invention relates to compounds according to formula (I), having the formula (I'-a) or (I'-b)



(I'-a)



(I'-b)

wherein R^1, R^2, R^3, R^4 and R^5 are as previously defined.

In an additional embodiment, R^1 is morpholin-4-yl.

In an additional embodiment, R^1 is pyridin-4-yl.

In an additional embodiment, R^1 is pyridin-3-yl.

In an additional embodiment, R^3 is hydrogen.

In an additional embodiment, R^2 is methyl and R^3 is hydrogen.

In an additional embodiment, Het is 3-pyridinyl or 4-pyridinyl.

In an additional embodiment, Het is *1H*-pyrazol-4-yl.

In an additional embodiment, R^4 is selected from ethyl; isopropyl; isobutyl; 2,2,2-trifluoroethyl; 2-hydroxy-2-methylpropyl; 2,2-difluoro-2-cyclopropylethyl; cyclopropyl; 2-methoxyethyl; (2*S*)-2-methoxypropyl; 2-ethoxyethyl; ethoxymethyl; 1-ethoxy-1-methylethyl; 1-methoxy-1-methylethyl; 2-methoxy-1,1-dimethylethyl; 3-methoxy-3-methylbutyl; 3-methoxypropyl; 2-methoxy-2-methyl-propyl; 2-methoxyethoxy; 2-methoxy-2-methyl-propoxy; tetrahydro-*2H*-pyran-4-yl; morpholin-4-yl; piperazin-1-yl; and (3*R*)-3-methoxypyrrolidin-1-yl.

In an additional embodiment, R^4 is selected from ethyl; isopropyl; isobutyl; 2-hydroxy-2-methylpropyl; cyclopropyl; 2-methoxyethyl; 2-ethoxyethyl; ethoxymethyl; 1-ethoxy-1-methylethyl; 1-methoxy-1-methylethyl; 2-methoxy-1,1-dimethylethyl; 3-methoxy-3-methylbutyl; 3-methoxypropyl; 2-methoxy-2-methylpropyl; 2-methoxyethoxy; 2-methoxy-2-methyl-propoxy; tetrahydro-*2H*-pyran-4-yl; morpholin-4-yl; piperazin-1-yl; and (3*R*)-3-methoxypyrrolidin-1-yl.

In an additional embodiment, R^4 is selected from ethyl; 2-hydroxy-2-methylpropyl; 2-methoxyethyl; 2-methoxy-2-methylpropyl; 2-methoxyethoxy; 2-methoxy-2-methyl-propoxy; and morpholin-4-yl.

In an additional embodiment, the invention relates to a compound according to formula (I'-a) of (I'-b) wherein

R^1 is morpholin-4-yl ;

R^2 is methyl ;

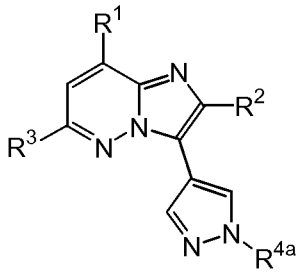
R^3 is hydrogen ;

Het is pyridin-3-yl ;

R^4 is 2-methoxyethyl ; and

R^5 is hydrogen.

In an additional embodiment, the invention relates to a compound according to formula (I'-c)



(I'-c)

wherein R^1, R^2, R^3 are as previously defined, R^{4a} is selected from the group consisting of R^{4a} is selected from the group consisting of hydrogen, C_{1-4}alkyl, trifluoromethylC_{0-4}alkyl, hydroxyC_{1-4}alkyl, difluorocyclopropylmethyl, cyclopropyldifluoroethyl, C_{3-8}cycloalkyl, C_{1-4}alkyloxyC_{1-5}alkyl, tetrahydropyranyl and pyridinylmethyl.

In an additional embodiment, R^{4a} is selected from hydrogen; isobutyl; 2,2,2-trifluoroethyl; (2,2-difluorocyclopropyl)methyl; 2,2-difluoro-2-cyclopropylethyl; 2-methoxyethyl; (2*S*)-2-methoxypropyl; 2-methoxy-2-methyl-propyl; tetrahydro-*2H*-pyran-4-yl; and (pyridin-3-yl)methyl.

In another embodiment, R^{4a} is selected from isobutyl; 2,2,2-trifluoroethyl; 2,2-difluoro-2-cyclopropylethyl; 2-methoxyethyl; (2*S*)-2-methoxypropyl; and 2-methoxy-2-methyl-propyl.

Particularly preferred compounds may be selected from the group of:
3-[6-(2-methoxyethyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 1),
3-[6-(3-methoxypropyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 2),
3-[6-(2-methoxy-2-methylpropyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 3),
3-[6-(2-methoxy-1,1-dimethylethyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 4),
3-[6-(1-ethoxy-1-methylethyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 5),
3-[6-(1-methoxy-1-methylethyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 6),
3-[6-(2-methoxy-2-methylpropyl)-3-pyridinyl]-2-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 7),
3-[6-(2-methoxyethoxy)-5-methyl-3-pyridinyl]-2-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 8),
3-[6-(2-methoxyethoxy)-3-pyridinyl]-2-methyl-8-(3-pyridinyl)-imidazo[1,2-b]pyridazine (compound 9),

2-cyclopropyl-3-[6-(2-methoxyethyl)-3-pyridinyl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 10),
3-[6-(2-methoxyethyl)-3-pyridinyl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 11),
2-methoxy-3-[6-(2-methoxyethyl)-3-pyridinyl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 12),
6-cyclopropyl-3-[6-(2-methoxyethyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 13),
6-cyclopropyl-3-[6-(2-methoxyethyl)-3-pyridinyl]-2-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 14),
2-cyclopropyl-3-[6-(2-methoxyethyl)-3-pyridinyl]-6-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 15),
3-[6-(2-methoxyethoxy)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 16),
3-[6-(ethoxymethyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 17),
3-[6-(2-methoxy-2-methylpropoxy)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 18),
2-methyl-8-(4-morpholinyl)-3-[6-(4-morpholinyl)-3-pyridinyl]-imidazo[1,2-b]pyridazine (compound 19),
3-[6-(2-methoxyethyl)-3-pyridinyl]-2-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 20),
3-[6-(2-methoxyethoxy)-3-pyridinyl]-2-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 21),
2-cyclopropyl-3-[6-(2-methoxyethyl)-3-pyridinyl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 22),
3-[6-(2-methoxyethyl)-3-pyridinyl]-2,6-dimethyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 23),
3-[6-(2-methoxyethyl)-3-pyridinyl]-2,6-dimethyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 24),
3-[6-(2-ethoxyethyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 25),
3-[2-(2-methoxyethyl)-4-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 26),
2-methyl-8-(4-morpholinyl)-3-[6-(tetrahydro-*2H*-pyran-4-yl)-3-pyridinyl]-imidazo[1,2-b]pyridazine (compound 27),
3-(6-ethyl-3-pyridinyl)-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 28),
3-[6-(3-methoxy-3-methylbutyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 29),

2-methyl-8-(4-morpholinyl)-3-[6-(1-piperazinyl)-3-pyridinyl]-imidazo[1,2-b]pyridazine (compound 30),
2-methyl-3-[6-(4-morpholinyl)-3-pyridinyl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 31),
2-methyl-3-[6-(1-methylethyl)-3-pyridinyl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 32),
3-(6-cyclopropyl-3-pyridinyl)-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 33),
3-[6-[(3*R*)-3-methoxy-1-pyrrolidinyl]-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 34),
2-methyl-3-[1-(2-methylpropyl)-*1H*-pyrazol-4-yl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 35),
3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 36),
3-[1-(2-methoxy-2-methylpropyl)-*1H*-pyrazol-4-yl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 37),
2-cyclopropyl-3-[1-(2-methoxy-2-methylpropyl)-*1H*-pyrazol-4-yl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 38),
2-methyl-3-(6-methyl-3-pyridinyl)-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 39),
6-cyclopropyl-3-[6-(2-methoxy-2-methylpropyl)-3-pyridinyl]-2-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 40),
6-cyclopropyl-3-[6-(2-methoxyethoxy)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 41),
6-cyclopropyl-3-[5-(2-methoxyethoxy)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 42),
6-cyclopropyl-3-[6-(2-methoxy-2-methylpropyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)- imidazo[1,2-b]pyridazine (compound 43),
2-cyclopropyl-3-[6-(2-methoxyethoxy)-3-pyridinyl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 44),
2-cyclopropyl-3-[6-(2-methoxy-2-methylpropyl)-3-pyridinyl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 45),
2-cyclopropyl-3-[6-(4-morpholinyl)-3-pyridinyl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 46),
3-[6-(2-methoxy-2-methylpropyl)-3-pyridinyl]-2,6-dimethyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 47),
3-[6-(2-methoxy-2-methylpropyl)-3-pyridinyl]-2,6-dimethyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 48),
3-[6-(2-methoxyethoxy)-3-pyridinyl]-2,6-dimethyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 49),

2-cyclopropyl-3-[6-(2-methoxy-2-methylpropyl)-3-pyridinyl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 50),
3-[6-(2-methoxy-2-methylpropyl)-3-pyridinyl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 51),
3-[6-(2-methoxyethoxy)-3-pyridinyl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 52),
2-cyclopropyl-3-[6-(2-methoxy-2-methylpropyl)-3-pyridinyl]-6-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 53),
5-[2-cyclopropyl-8-(4-morpholinyl)imidazo[1,2-b]pyridazin-3-yl]-α,α-dimethyl-2-pyridineethanol (compound 54),
2-cyclopropyl-3-[6-(2-methoxy-2-methylpropyl)-3-pyridinyl]-6-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 55),
2-cyclopropyl-3-[6-(2-methoxyethyl)-3-pyridinyl]-6-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 56),
3-[6-(2-methoxyethyl)-3-pyridinyl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 57),
6-cyclopropyl-2-methyl-3-[6-(4-morpholinyl)-3-pyridinyl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 58),
6-cyclopropyl-3-[6-(2-methoxyethoxy)-3-pyridinyl]-2-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 59),
3-[6-(2-methoxy-2-methylpropyl)-3-pyridinyl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 60),
3-[6-(4-morpholinyl)-3-pyridinyl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 61),
2-methyl-8-(4-morpholinyl)-3-[6-(2,2,2-trifluoroethoxy)-3-pyridinyl]-imidazo[1,2-b]pyridazine (compound 62),
2-methyl-8-(4-morpholinyl)-3-[6-(trifluoromethyl)-3-pyridinyl]-imidazo[1,2-b]pyridazine (compound 63),
3-[6-(2-methoxyethyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-6-(trifluoromethyl)-imidazo[1,2-b]pyridazine (compound 64),
3-[6-(cyclopropylmethoxy)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 65),
2-methyl-3-[6-(1-methylethoxy)-3-pyridinyl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 66),
2-methyl-3-[2-(1-methylethoxy)-4-pyridinyl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 67),
2,6-dimethyl-8-(4-morpholinyl)-3-[6-(4-morpholinyl)-3-pyridinyl]-imidazo[1,2-b]pyridazine (compound 68),
3-[6-(2-methoxyethoxy)-3-pyridinyl]-2,6-dimethyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 69),

2,6-dimethyl-3-[6-(4-morpholinyl)-3-pyridinyl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 70),
2-cyclopropyl-6-methyl-3-[6-(4-morpholinyl)-3-pyridinyl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 71),
2-cyclopropyl-3-[6-(2-methoxyethoxy)-3-pyridinyl]-6-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 72),
2-cyclopropyl-3-[6-(2-methoxyethoxy)-3-pyridinyl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 73),
2-cyclopropyl-3-[6-(2-methoxyethoxy)-3-pyridinyl]-6-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 74),
2-cyclopropyl-6-methyl-8-(4-morpholinyl)-3-[6-(4-morpholinyl)-3-pyridinyl]-imidazo[1,2-b]pyridazine (compound 75),
2-methyl-3-[6-[2-(1-methylethoxy)ethyl]-3-pyridinyl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 76),
2-methyl-8-(4-morpholinyl)-3-[6-[2-(1-pyrrolidinyl)ethyl]-3-pyridinyl]-imidazo[1,2-b]pyridazine (compound 77),
6-cyclopropyl-2-methyl-8-(4-morpholinyl)-3-[6-(tetrahydro-*2H*-pyran-4-yl)-3-pyridinyl]-imidazo[1,2-b]pyridazine (compound 78),
2-cyclopropyl-6-methyl-8-(4-morpholinyl)-3-[6-(tetrahydro-*2H*-pyran-4-yl)-3-pyridinyl]-imidazo[1,2-b]pyridazine (compound 79),
2-cyclopropyl-6-methyl-8-(4-pyridinyl)-3-[6-(tetrahydro-*2H*-pyran-4-yl)-3-pyridinyl]-imidazo[1,2-b]pyridazine (compound 80),
6-cyclopropyl-2-methyl-8-(4-pyridinyl)-3-[6-(tetrahydro-*2H*-pyran-4-yl)-3-pyridinyl]- imidazo[1,2-b]pyridazine (compound 81),
8-(4-morpholinyl)-3-[6-(tetrahydro-*2H*-pyran-4-yl)-3-pyridinyl]-imidazo[1,2-b]pyridazine (compound 82),
3-(6-ethyl-3-pyridinyl)-2-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 83),
2-cyclopropyl-3-(6-ethyl-3-pyridinyl)-6-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 84),
2-cyclopropyl-3-[6-(2-methoxyethyl)-3-pyridinyl]-8-(4-morpholinyl)-6-(trifluoromethyl)-imidazo[1,2-b]pyridazine (compound 85),
6-cyclopropyl-3-(6-ethyl-3-pyridinyl)-2-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 86),
2-cyclopropyl-3-(6-ethyl-3-pyridinyl)-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 87),
3-(6-ethyl-3-pyridinyl)-2,6-dimethyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 88),
2-methyl-8-(4-morpholinyl)-3-[6-(1-pyrrolidinyl)-3-pyridinyl]-imidazo[1,2-b]pyridazine (compound 89),

N-(1-methylethyl)-5-[2-methyl-8-(4-morpholinyl)imidazo[1,2-b]pyridazin-3-yl]-2-pyridinamine (compound 90),
2-methyl-8-(4-morpholinyl)-3-[2-(4-morpholinyl)-4-pyridinyl]-imidazo[1,2-b]pyridazine (compound 91),
2-methyl-8-(4-morpholinyl)-3-[2-(1-pyrrolidinyl)-4-pyridinyl]-imidazo[1,2-b]pyridazine (compound 92),
N-(1-methylethyl)-4-[2-methyl-8-(4-morpholinyl)imidazo[1,2-b]pyridazin-3-yl]-2-pyridinamine (compound 93),
6-cyclopropyl-2-methyl-8-(4-morpholinyl)-3-[6-(4-morpholinyl)-3-pyridinyl]-imidazo[1,2-b]pyridazine (compound 94),
2-cyclopropyl-8-(4-morpholinyl)-3-[6-(4-morpholinyl)-3-pyridinyl]-imidazo[1,2-b]pyridazine (compound 95),
2,6-dimethyl-3-[6-(1-piperazinyl)-3-pyridinyl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 96),
2-methyl-3-[6-(1-piperazinyl)-3-pyridinyl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 97),
2-cyclopropyl-8-(4-morpholinyl)-3-[6-(1-piperazinyl)-3-pyridinyl]-imidazo[1,2-b]pyridazine (compound 98),
6-cyclopropyl-2-methyl-3-[6-(1-piperazinyl)-3-pyridinyl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 99),
2-cyclopropyl-6-methyl-8-(4-morpholinyl)-3-[6-(1-piperazinyl)-3-pyridinyl]-imidazo[1,2-b]pyridazine (compound 100),
2-cyclopropyl-6-methyl-3-[6-(1-piperazinyl)-3-pyridinyl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 101),
2-cyclopropyl-3-[6-(1-piperazinyl)-3-pyridinyl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 102),
2-methyl-8-(4-morpholinyl)-3-[2-(1-piperazinyl)-4-pyridinyl]-imidazo[1,2-b]pyridazine (compound 103),
2-methyl-3-[6-(2-methylpropyl)-3-pyridinyl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 104),
2-methyl-3-[2-(2-methylpropyl)-4-pyridinyl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 105),
2-cyclopropyl-3-(6-ethyl-3-pyridinyl)-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 106),
6-cyclopropyl-3-(6-ethyl-3-pyridinyl)-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 107),
3-(6-ethyl-3-pyridinyl)-2,6-dimethyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 108),
3-(6-ethyl-3-pyridinyl)-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 109),

3-(6-cyclopropyl-3-pyridinyl)-2,6-dimethyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 110),
3-(6-cyclopropyl-3-pyridinyl)-2-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 111),
3-(6-cyclopropyl-3-pyridinyl)-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 112),
3-[6-[(3S)-3-methoxy-1-pyrrolidinyl]-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 113),
3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-2-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 114),
2-methyl-8-(4-morpholinyl)-3-[1-(3-pyridinylmethyl)-*1H*-pyrazol-4-yl]-imidazo[1,2-b]pyridazine (compound 115),
2-methyl-8-(4-morpholinyl)-3-(*1H*-pyrazol-4-yl)-imidazo[1,2-b]pyridazine (compound 116),
2-methyl-8-(4-morpholinyl)-3-[1-(tetrahydro-*2H*-pyran-4-yl)-*1H*-pyrazol-4-yl]-imidazo[1,2-b]pyridazine (compound 117),
3-{1-[(2,2-difluorocyclopropyl)methyl]-*1H*-pyrazol-4-yl}-2-methyl-8-morpholin-4-ylimidazo[1,2-*b*]pyridazine (compound 118),
2-cyclopropyl-3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 119),
3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-2-(1-methylethyl)-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 120),
3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-2-(1-methylethyl)-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 121),
3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-8-(4-pyridinyl)-2-(trifluoromethyl)-imidazo[1,2-b]pyridazine (compound 122),
3-[1-(2-methoxy-2-methylpropyl)-*1H*-pyrazol-4-yl]-2-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 123),
2-methyl-3-[1-(2-methylpropyl)-*1H*-pyrazol-4-yl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 124),
6-cyclopropyl-3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 125),
6-cyclopropyl-3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-2-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 126),
2-ethyl-3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 127),
3-[1-(2-cyclopropyl-2,2-difluoroethyl)-*1H*-pyrazol-4-yl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 128),
3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-2-methyl-8-(4-pyridinyl)-6-(trifluoromethyl)-imidazo[1,2-b]pyridazine (compound 129),

3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-2-methyl-8-(4-morpholinyl)-6-(trifluoromethyl)-imidazo[1,2-b]pyridazine (compound 130),
3-[1-[(2S)-2-methoxypropyl]-*1H*-pyrazol-4-yl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 131),
2-ethyl-3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 132),
3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-2,6-dimethyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 133),
3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-2,6-dimethyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 134),
2-methyl-8-(4-pyridinyl)-3-[1-(2,2,2-trifluoroethyl)-*1H*-pyrazol-4-yl]-imidazo[1,2-b]pyridazine (compound 135),
3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-2-methyl-8-(1-pyrrolidinyl)-imidazo[1,2-b]pyridazine (compound 136),
2-methyl-8-(4-morpholinyl)-3-[1-(2,2,2-trifluoroethyl)-*1H*-pyrazol-4-yl]-imidazo[1,2-b]pyridazine (compound 137),
2-cyclopropyl-8-(4-morpholinyl)-3-[1-(2,2,2-trifluoroethyl)-*1H*-pyrazol-4-yl]-imidazo[1,2-b]pyridazine (compound 138),
3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-8-(4-morpholinyl)-2-(trifluoromethyl)-imidazo[1,2-b]pyridazine (compound 139),
2-methoxy-3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 140),
2-cyclopropyl-8-(4-pyridinyl)-3-[1-(2,2,2-trifluoroethyl)-*1H*-pyrazol-4-yl]-imidazo[1,2-b]pyridazine (compound 141),
2-cyclopropyl-3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 142),
2-cyclopropyl-3-[1-(2-methoxy-2-methylpropyl)-*1H*-pyrazol-4-yl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 143),
8-(4-morpholinyl)-3-[6-(4-morpholinyl)-3-pyridinyl]-imidazo[1,2-b]pyridazine (compound 144),
3-[6-(2-methoxyethyl)-3-pyridinyl]-8-(4-morpholinyl)-2-(trifluoromethyl)-imidazo[1,2-b]pyridazine (compound 145),
6-chloro-2-methyl-8-(4-morpholinyl)-3-[1-(2,2,2-trifluoroethyl)-*1H*-pyrazol-4-yl]-imidazo[1,2-b]pyridazine (compound 146),
6-chloro-3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-2-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 147),
2-cyclopropyl-3-[1-(2-methylpropyl)-*1H*-pyrazol-4-yl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 148), and
3-[5-(2-methoxyethoxy)-3-pyridinyl]-2-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 149),

and the stereoisomeric forms, the pharmaceutically acceptable salts and the solvates thereof.

More preferred particular compounds are compounds 1 to 38, and pharmaceutically acceptable salts thereof.

Other particularly preferred compounds include
3-[6-(2-methoxyethyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine hydrochloride (compound 1a),
3-[6-(2-methoxyethyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine maleate (compound 1b),
3-[6-(2-methoxyethyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine monohydrate (compound 1c),
3-[6-(2-methoxyethoxy)-3-pyridinyl]-2-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine hydrochloride (compound 21a),
2-cyclopropyl-3-[6-(2-methoxy-2-methylpropyl)-3-pyridinyl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine hydrochloride (compound 45a),
3-[6-(2-methoxy-2-methylpropyl)-3-pyridinyl]-2,6-dimethyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 48),
2-cyclopropyl-3-[6-(2-methoxy-2-methylpropyl)-3-pyridinyl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 50),
5-[2-cyclopropyl-8-(4-morpholinyl)imidazo[1,2-b]pyridazin-3-yl]-α,α-dimethyl-2-pyridineethanol (compound 54),
3-[6-(4-morpholinyl)-3-pyridinyl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 61),
2,6-dimethyl-8-(4-morpholinyl)-3-[6-(4-morpholinyl)-3-pyridinyl]-imidazo[1,2-b]pyridazine (compound 68),
2-cyclopropyl-6-methyl-3-[6-(4-morpholinyl)-3-pyridinyl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 71),
2-cyclopropyl-3-[6-(2-methoxyethoxy)-3-pyridinyl]-6-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 72),
2-methyl-8-(4-morpholinyl)-3-[2-(4-morpholinyl)-4-pyridinyl]-imidazo[1,2-b]pyridazine (compound 91),
3-{1-[(2,2-difluorocyclopropyl)methyl]-*1H*-pyrazol-4-yl}-2-methyl-8-morpholin-4-ylimidazo[1,2-*b*]pyridazine (compound 118),
2-methyl-3-[1-(2-methylpropyl)-*1H*-pyrazol-4-yl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 124),
6-cyclopropyl-3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 125),

2-ethyl-3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 127),
3-[1-[(2S)-2-methoxypropyl]-*1H*-pyrazol-4-yl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 131),
3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-2,6-dimethyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 133),
3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-2,6-dimethyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 134),
2-methyl-8-(4-pyridinyl)-3-[1-(2,2,2-trifluoroethyl)-*1H*-pyrazol-4-yl]-imidazo[1,2-b]pyridazine (compound 135),
2-cyclopropyl-3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 142),
2-cyclopropyl-3-[1-(2-methoxy-2-methylpropyl)-*1H*-pyrazol-4-yl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 143),
6-chloro-3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-2-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 147), and
2-cyclopropyl-3-[1-(2-methylpropyl)-*1H*-pyrazol-4-yl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 148),

and the stereoisomeric forms, the pharmaceutically acceptable salts and the solvates thereof.

For therapeutic use, salts of the compounds of formula (I) are those wherein the counterion is pharmaceutically acceptable. However, salts of acids and bases which are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not, are included within the ambit of the present invention.

The pharmaceutically acceptable salts are defined to comprise the therapeutically active non-toxic acid addition salt forms that the compounds according to Formula (I) are able to form. Said salts can be obtained by treating the base form of the compounds according to Formula (I) with appropriate acids, for example inorganic acids, for example hydrohalic acids, in particular hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid and phosphoric acid; organic acids, for example acetic acid, hydroxyacetic acid, propanoic acid, lactic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, cyclamic acid, salicylic acid, *p*-aminosalicylic acid and pamoic acid.

Conversely, said salt forms can be converted into the free base form by treatment

with an appropriate base.

The compounds according to Formula (I) containing acidic protons may also be converted into their therapeutically active non-toxic base salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkaline and alkaline earth metal salts, in particular lithium, sodium, potassium, magnesium and calcium salts, salts with organic bases, e.g. primary, secondary and tertiary aliphatic and aromatic amines such as methylamine, ethylamine, propylamine, isopropylamine, the four butylamine isomers, dimethylamine, diethylamine, diethanolamine, dipropylamine, diisopropylamine, di-n-butylamine, pyrrolidine, piperidine, morpholine, trimethylamine, triethylamine, tripropylamine, quinuclidine, pyridine, quinoline, and isoquinoline, the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids, for example arginine and lysine.

Conversely, said salt forms can be converted into the free acid forms by treatment with an appropriate acid.

The term solvate comprises the solvent addition forms as well as the salts thereof, which the compounds of formula (I) are able to form. Examples of such solvent addition forms are e.g. hydrates, alcoholates and the like.

The term "stereochemically isomeric forms" or "stereoisomeric forms" as used hereinbefore defines all the possible isomeric forms that the compounds of Formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. The invention also embraces each of the individual isomeric forms of the compounds of Formula (I) and their salts and solvates, substantially free, *i.e.* associated with less than 10%, preferably less than 5%, in particular less than 2% and most preferably less than 1%, of the other isomers. Thus, when a compound of formula (I) is for instance specified as (R), this means that the compound is substantially free of the (S) isomer. Stereogenic centers may have the R- or S-configuration; substituents on bivalent cyclic (partially) saturated radicals may have either the cis- or trans-configuration.

Following CAS nomenclature conventions, when two stereogenic centers of known absolute configuration are present in a compound, an *R* or *S* descriptor is assigned (based on Cahn-Ingold-Prelog sequence rule) to the lowest-numbered chiral center, the reference center. The configuration of the second stereogenic center is indicated using relative descriptors [*R**,*R**] or [*R**,*S**], where R* is always specified as the reference center and [*R**,*R**] indicates centers with the same chirality and [*R**,*S**]

indicates centers of unlike chirality. For example, if the lowest-numbered chiral center in the compound has an *S* configuration and the second center is *R*, the stereo descriptor would be specified as *S*-[*R**,*S**].

In the framework of this application, an element, in particular when mentioned in relation to a compound according to Formula (I), comprises all isotopes and isotopic mixtures of this element, either naturally occurring or synthetically produced, either with natural abundance or in an isotopically enriched form. Radiolabelled compounds of Formula (I) may comprise a radioactive isotope selected from the group of ^{3}H, ^{11}C, ^{18}F, ^{122}I, ^{123}I, ^{125}I, ^{131}I, ^{75}Br, ^{76}Br, ^{77}Br and ^{82}Br. Preferably, the radioactive isotope is selected from the group of ^{3}H, ^{11}C and ^{18}F.

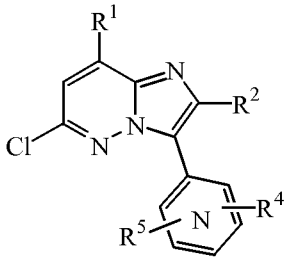
Preparation

The compounds according to the invention can generally be prepared by a succession of steps, each of which is known to the skilled person. In particular, the compounds can be prepared according to the following synthesis methods.

The compounds of Formula (I) may be synthesized in the form of racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of Formula (I) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of Formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically.

A. Preparation of the final compounds

A compound of Formula (I) wherein R^1, R^2, R^4 and R^5 are as defined before, R^3 is hydrogen and Het is pyridinyl, can be prepared by reacting a compound of Formula (Ia)

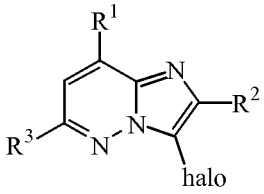


(Ia)

wherein R^1, R^2, R^4 and R^5 are as defined before, with hydrogen in the presence of a suitable catalyst, such as 10% palladium on charcoal, in a suitable inert solvent, such as methanol or ethanol, under suitable reaction conditions, such as a convenient temperature, typically ranging between 25 °C and 40 °C or with ammonium formate in the presence of a suitable catalyst such as 10% palladium on charcoal, in a suitable inert solvent, such as methanol, ethanol, ethyl acetate or dichloromethane or mixtures thereof, under suitable reaction conditions, such as heating at a convenient temperature, typically ranging between 40 °C and 100 °C.

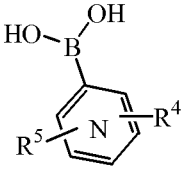
A compound of Formula (I) wherein R^1, R^2, R^4 and R^5 are as defined before, R^3 is C_{1-4}alkyl or C_{3-8}cycloalkyl and Het is pyridinyl can be prepared by reacting a compound of Formula (Ia) wherein R^1, R^2, R^4 and R^5 are as defined before, with a boronic acid derivative of Formula $R^3B(OH)_2$ wherein R^3 is C_{1-4}alkyl or C_{3-8}cycloalkyl, in the presence of a suitable catalyst, such as tetrakis(triphenylphosphine)palladium (0) or palladium (II) acetate, in the presence of a suitable phosphine ligand, such as 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, in the presence of a suitable base, such as sodium carbonate or potassium phosphate, in a suitable inert solvent, such as a mixture of 1,4-dioxane and water or toluene, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

Alternatively, compounds of Formula (I) wherein R^1, R^2, R^3, R^4 and R^5 are as defined before and Het is pyridinyl, can also be prepared by reacting an intermediate of Formula (II)



(II)

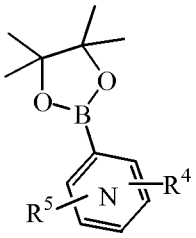
wherein R^1, R^2 and R^3 are as defined before and halo represents a bromo or iodo, with a boronic acid derivative of Formula (III)



(III)

where R^4 and R^5 are as defined before, in the presence of a suitable catalyst, such as tetrakis(triphenylphosphine)palladium (0), in the presence of a suitable base, such as sodium carbonate, in a suitable inert solvent, such as a mixture of 1,4-dioxane and water, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

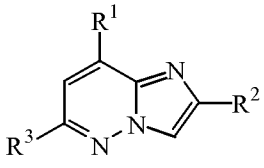
Compounds of Formula (I) wherein R^1, R^2, R^3, R^4 and R^5 are as defined before and Het is pyridinyl, can also be prepared by reacting an intermediate of Formula (II) wherein R^1, R^2 and R^3 are as defined before and halo represents a bromo or iodo, with a boronate derivative of Formula (IV)



(IV)

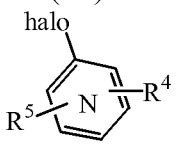
where R^4 and R^5 are as defined before, in the presence of a suitable catalyst, such as tetrakis(triphenylphosphine)palladium (0), in the presence of a suitable base, such as sodium carbonate, in a suitable inert solvent, such as a mixture of 1,4-dioxane and water, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

Compounds of Formula (I) wherein R^1, R^2, R^3, R^4 and R^5 are as defined before and Het is pyridinyl, can also be prepared by reacting an intermediate of Formula (V)



(V)

with a halopyridine of Formula (VI)

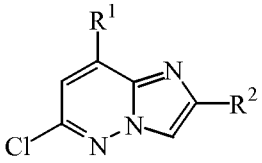


(VI)

where R^4 and R^5 are as defined before and halo is bromo or iodo, in the presence of a suitable catalyst, such as palladium (II) acetate, in the presence of a suitable phosphine ligand, such as butyldi-1-adamantylphosphine, in the presence of a suitable base, such as potassium phosphate, in a suitable inert solvent, such as *N*,*N*-dimethylformamide or *N*-methylpyrrolidine, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

A compound of Formula (II) wherein R^1, R^2 and R^3 are as defined before, except when simultaneously R^1 is NR^6R^7, R^2 is trifluoromethyl and R^3 is chloro, and halo represents a bromo or iodo, can be prepared by reacting a compound of Formula (V) wherein R^1, R^2 and R^3 are as defined before, with *N*-bromo- or *N*-iodosuccinimide, in a suitable inert solvent, such as dichloromethane, in the presence of a suitable acid catalyst, such as acetic acid, under suitable reaction conditions, such as a convenient temperature, typically ranging between -10 °C and 40 °C.

A compound of Formula (V) wherein R^1 and R^2 are as defined before and R^3 is hydrogen, can also be prepared by reacting a compound of Formula (Va)



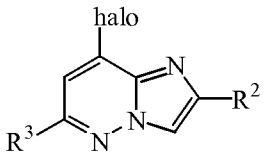
(Va)

wherein R^1 and R^2 are as defined before, with hydrogen in the presence of a suitable catalyst, such as 10% palladium on charcoal, in the presence of a suitable base, such as triethylamine, in a suitable inert solvent, such as methanol or ethanol, under suitable reaction conditions, such as a convenient temperature, typically ranging between 25 °C and 40 °C or with ammonium formate in the presence of a suitable catalyst such as 10% palladium on charcoal, in a suitable inert solvent, such as methanol, ethanol, ethyl acetate or dichloromethane or mixtures thereof, under suitable reaction conditions, such as heating at a convenient temperature, typically ranging between 40 °C and 100 °C.

A compound of Formula (V) wherein R^1 and R^2 are as defined before, and R^3 is C_{1-4}alkyl or C_{3-8}cycloalkyl can be prepared by reacting a compound of Formula (Va) wherein R^1 and R^2 are as defined before with a boronic acid derivative of Formula $R^3B(OH)_2$ where R^3 is C_{1-4}alkyl or C_{3-8}cycloalkyl, in the presence of a suitable catalyst, such as tetrakis(triphenylphosphine)palladium (0) or palladium (II) acetate, in the

presence of a suitable phosphine ligand, such as 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, in the presence of a suitable base, such as sodium carbonate or potassium phosphate, in a suitable inert solvent, such as a mixture of 1,4-dioxane and water or toluene, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

A compound of Formula (V) wherein R^1 is pyridinyl, pyridinyl optionally substituted with halogen, C_{1-4}alkyl, trifluoromethyl or C_{1-4}alkyloxy, R^2 is hydrogen, C_{1-4}alkyl, trifluoromethyl or C_{3-8}cycloalkyl and R^3 is chloro or trifluoromethyl, can be prepared by reacting a compound of Formula (VII)

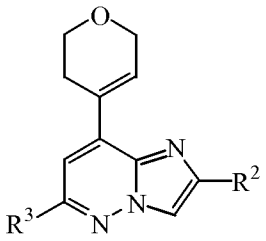


(VII)

where R^2 is as described before, R^3 is chloro or trifluoromethyl and halo represents chloro, bromo or iodo, with a boronic acid derivative of Formula $R^1B(OH)_2$ wherein R^1 is pyridinyl or pyridinyl optionally substituted with halogen, C_{1-4}alkyl, trifluoromethyl or C_{1-4}alkyloxy, in the presence of a suitable catalyst, such as tetrakis(triphenylphosphine)palladium (0), in the presence of a suitable base, such as sodium carbonate, in a suitable inert solvent, such as a mixture of 1,4-dioxane and water, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

A compound of Formula (V) wherein R^1 is NR^6R^7, R^2 is as described before, R^3 is chloro or trifluoromethyl and R^6 and R^7 are as defined before, can be prepared by reacting a compound of Formula (VII) where R^2 is as described before, R^3 is chloro or trifluoromethyl and halo represents chloro, bromo or iodo with a compound of Formula R^6R^7NH wherein R^6 and R^7 are as defined before, in a suitable inert solvent, such as acetonitrile, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

Compounds of Formula (V) wherein R^1 is tetrahydropyranyl, R^2 is as defined before and R^3 is chloro or trifluoromethyl, can be prepared by reacting a compound of Formula (VIII)



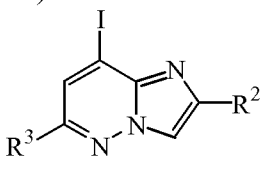
(VIII)

wherein R^2 is as defined before and R^3 is chloro or trifluoromethyl, with hydrogen in the presence of a suitable catalyst, such as 10% palladium on charcoal, in a suitable inert solvent, such as methanol or ethanol, under suitable reaction conditions, such as a convenient temperature, typically ranging between 25 °C and 40 °C or with ammonium formate in the presence of a suitable catalyst such as 10% palladium on charcoal, in a suitable inert solvent, such as methanol, ethanol, ethyl acetate or dichloromethane or mixtures thereof, under suitable reaction conditions, such as heating at a convenient temperature, typically ranging between 40 °C and 100 °C.

A compound of Formula (VIII) where R^2 is as defined before and R^3 is chloro or trifluoromethyl, can be prepared by reacting a compound of Formula (VII) where R^2 is as defined before, R^3 is chloro or trifluoromethyl and halo represents chloro, bromo or iodo with 3,6-dihydro-*2H*-pyran-4-boronic acid pinacol ester, in the presence of a suitable catalyst, such as tetrakis(triphenylphosphine)palladium (0), in the presence of a suitable base, such as sodium carbonate, in a suitable inert solvent, such as a mixture of 1,4-dioxane and water, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

3,6-Dihydro-*2H*-pyran-4-boronic acid pinacol ester can be obtained by procedures similar to those described in, Qiu, Y. et al. WO 2004075846 A2.

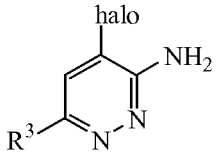
A compound of Formula (VIIa)



(VIIa)

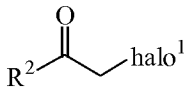
where R^2 is hydrogen, C_{1-4}alkyl, trifluoromethyl or C_{3-8}cycloalkyl and R^3 is chloro or trifluoromethyl can be prepared by reacting an intermediate of Formula (VII) wherein R^2 is hydrogen, C_{1-4}alkyl, trifluoromethyl or C_{3-8}cycloalkyl, R^3 is chloro or trifluoromethyl and halo represents chloro or bromo with sodium iodide, in the presence of a suitable acidic catalyst, such as hydriodic acid, in a suitable inert solvent, such as acetonitrile, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

A compound of Formula (VII) where R^2 is hydrogen, C_{1-4}alkyl, trifluoromethyl or C_{3-8}cycloalkyl, R^3 is chloro or trifluoromethyl and halo represents chloro or bromo, can be prepared by reacting a compound of Formula (IX)



(IX)

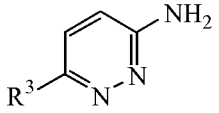
wherein R^3 is chloro or trifluoromethyl and halo represents chloro or bromo, with a compound of Formula (X)



(X)

wherein R^2 is hydrogen, C_{1-4}alkyl, trifluoromethyl or C_{3-8}cycloalkyl and halo^1 represents chloro or bromo, either neat or in a suitable inert solvent, such as ethanol, isopropanol or 1,2-dimethoxyethane, under suitable reaction conditions, such as heating at a convenient temperature either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

A compound of Formula (IX) where R^3 is chloro or trifluoromethyl and halo represents bromo, can be prepared by reacting an aminopyridazine of Formula (XI)



(XI)

with bromine, in the presence of a suitable base, such as sodium hydrogen carbonate, in a suitable inert solvent, such as methanol, under suitable reaction conditions, such as a convenient temperature, typically ranging between -10 °C and 25 °C.

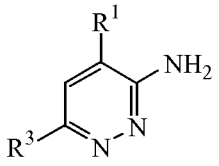
A compound of Formula (IX) where R^3 is chloro or trifluoromethyl and halo represents chloro, can be obtained from an aminopyridazine of Formula (XI) by procedures similar to those described in Dewdney, N. et al. WO 2009077334 A1.

A compound of Formula (X) wherein R^2 is hydrogen, C_{1-4}alkyl, trifluoromethyl or C_{3-8}cycloalkyl and halo represents chloro or bromo, can be obtained commercially or can be prepared by procedures similar to those described in Gaudry, M.; Marquet, A. Organic Syntheses. 1976, 55.

A compound of Formula (XI) where R^3 is chloro can be obtained commercially.

A compound of Formula (XI) where R^3 is trifluoromethyl can be obtained by procedures similar to those described in De Bruyn, M. F. L. et al. WO 2007048779 A1.

A compound of Formula (V) wherein R^1 is NR^6R^7, R^2 is C_{1-4}alkyloxy and R^3 is chloro or trifluoromethyl and R^6 and R^7 are as defined before, can be prepared by reacting an intermediate of Formula (XII)



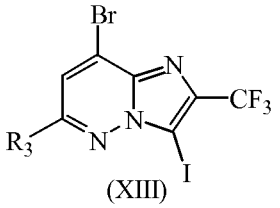
(XII)

wherein R^1 is NR^6R^7, R^3 is chloro or trifluoromethyl and R^6 and R^7 are as defined before, with a reagent of Formula (X) wherein R^2 is C_{1-4}alkyloxy and and halo^1 represents chloro or bromo, in a suitable inert solvent, such as methanol, under suitable reaction conditions, such as heating at a convenient temperature either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

Compounds of Formula (XII) wherein R^1 is NR^6R^7, R^3 is chloro or trifluoromethyl and R^6 and R^7 are as defined before can be prepared by reacting a compound of Formula (IX) where R^3 is chloro or trifluoromethyl and halo represents chloro or bromo with a derivative compound of formula R^6R^7NH wherein R^6 and R^7 are as defined before, in a suitable inert solvent, such as acetonitrile, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

Compounds of Formula (IX) can be obtained as described before.

A compound of Formula (II) wherein R^1 is NR^6R^7, R^2 is trifluoromethyl, R^3 is chloro or trifluoromethyl, and halo represents a iodo, can be prepared by reacting a compound of Formula (XIII)



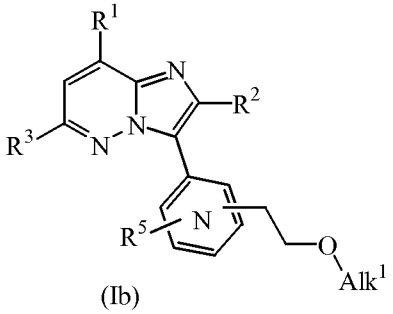
(XIII)

wherein R^3 is chloro or trifluoromethyl with a compound of formula R^6R^7NH, where R^6 and R^7 are as defined before in the presence of a suitable base, such as *N*,*N*-diisopropylethylamine, in a suitable solvent, such as acetonitrile, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

A compound of Formula (XIII), where R^3 is chloro or trifluoromethyl can be prepared by reacting a compound of Formula (VII) where R^2 is trifluoromethyl, R^3 is chloro or trifluoromethyl and halo represents a bromo, with *N*-iodosuccinimide, in a suitable inert solvent, such as dichlorometane, in the presence of a suitable acid catalyst, such as trifluoroacetic acid, under suitable reaction conditions, such as a convenient temperature, typically ranging between -10 °C and 60 °C.

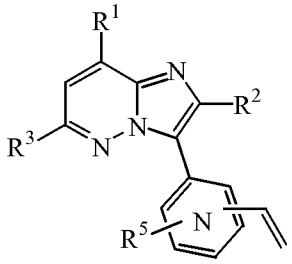
A compound of Formula (VII) where R^2 is trifluoromethyl, R^3 is chloro or trifluoromethyl and halo represents a bromo, can be obtained as described before.

A compound of Formula (Ib)



(Ib)

wherein R^1, R^2, R^3 and R^5 are as defined before, R^4 is Alk^1-oxyethyl and Alk^1 is C_{1-4}alkyl, can be prepared by reacting a compound of Formula (XIV)



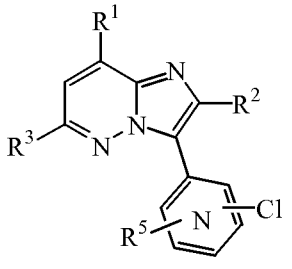
(XIV)

where R^1, R^2, R^3 and R^5 are as defined before with an alcohol of Formula Alk^1-OH wherein Alk^1 is C_{1-4}alkyl in the presence of a suitable base, such as the sodium or potassium salt of the corresponding alcohol, in a suitable solvent, such as the corresponding alcohol, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

Alternatively, a compound of Formula (Ib) wherein R^1, R^2, R^3 and R^5 are as defined before, R^4 is Alk^1-oxyethyl and Alk^1 is C_{1-4}alkyl, can be prepared by reacting a compound of Formula (XIV), where R^1, R^2, R^3 and R^5 are as defined before with an alcohol of Formula Alk^1-OH wherein Alk^1 is C_{1-4}alkyl, in the presence of a suitable acid, such as potassium hydrogensulfate, in a suitable solvent, such as the corresponding alcohol, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

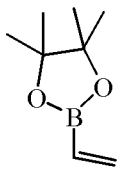
An alcohol of Formula Alk^1-OH wherein Alk^1 is C_{1-4}alkyl can be obtained commercially or alternatively can also be obtained by procedures similar to those described in Morel, P. US 2008102028 A1.

A compound of Formula (XIV) where R^1, R^2, R^3 and R^5 are as defined before can be prepared by reacting a compound of Formula (XV)



(XV)

wherein R^1, R^2, R^3 and R^5 are as defined before, with a compound of Formula (XVI)

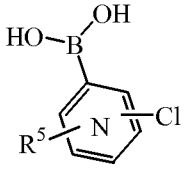


(XVI)

in the presence of a suitable catalyst, such as tetrakis(triphenylphosphine)palladium (0), in the presence of a suitable base, such as sodium carbonate, in a suitable inert solvent, such as a mixture of 1,4-dioxane and water, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

Vinylboronic acid pinacol ester, of Formula (XVI), can be obtained commercially.

A compound of Formula (XV) where R^1, R^2, R^3 and R^5 are as defined before, can be prepared by reacting a compound of Formula (II) wherein R^1, R^2 and R^3 are as defined before and halo is bromo or iodo, with a boronic acid derivative of Formula (XVII)

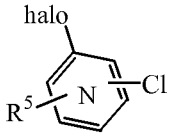


(XVII)

where R^5 is as defined before, in the presence of a suitable catalyst, such as tetrakis(triphenylphosphine)palladium (0), in the presence of a suitable base, such as sodium carbonate, in a suitable inert solvent such as a mixture of 1,4-dioxane and water, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

Compounds of Formula (II) can be obtained as described before.

A boronic acid derivative of Formula (XVII) where R^5 is as defined before, can be obtained commercially or alternatively can be prepared by reacting a compound of Formula (XVIII)



(XVIII)

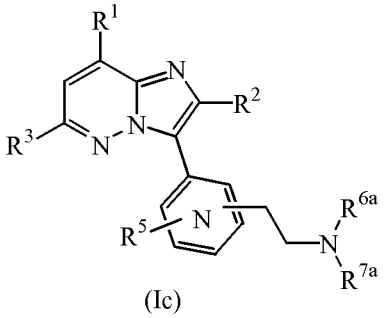
where R^5 is as defined before and halo represents a bromo or iodo, with triisopropyl borate, in the presence of a suitable base, such as *n*-butyllithium in the presence of a suitable diamine such as *N*,*N*,*N*',*N*'-tetramethylenediamine, in a suitable inert solvent such as diethylether, under suitable reaction conditions, such as a convenient temperature, typically ranging between -78°C and 25°C.

A halopyridine of Formula (XVIII) where R^5 is as defined before and halo is bromo or iodo, can be obtained commercially.

Alternatively, a compound of Formula (XV) where R^1, R^2, R^3 and R^5 are as defined before, can be prepared by reacting a compound of Formula (V) wherein R^1, R^2 and R^3 are as defined before with a halopyridine of Formula (XVIII), where R^5 is as defined before and halo represents a bromo or iodo, in the presence of a suitable catalyst, such as palladium (II) acetate, in the presence of a suitable phosphine ligand, such as butyldi-1-adamantylphosphine, in the presence of a suitable base, such as potassium phosphate, in a suitable inert solvent, such as *N*,*N*-dimethylformamide, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

Compounds of Formula (V) can be obtained as described before.

Compounds of Formula (Ic)



(Ic)

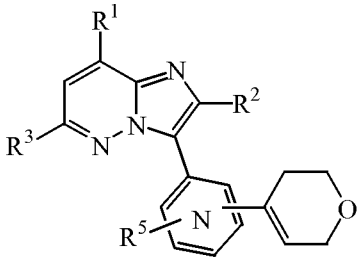
wherein R^1, R^2, R^3 and R^5 are as defined before, R^4 is $NR^{6a}R^{7a}$ethyl and R^{6a} and R^{7a} are as defined before, can be prepared by reacting a compound of Formula (XIV) where R^1, R^2, R^3 and R^5 are as defined before with a reagent of Formula $R^{6a}R^{7a}NH$ where R^{6a} and R^{7a} are as defined before in the presence of a suitable base, such as sodium *tert*-butoxide, in a suitable solvent, such as tetrahydrofuran, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating

or under microwave irradiation for a period of time to ensure the completion of the reaction.

A reagent of Formula R^6R^7NH or $R^{6a}R^{7a}NH$, wherein R^6, R^{6a}, R^7 and R^{7a} are as defined before, can be obtained commercially.

Compounds of Formula (I) where R^1, R^2, R^3 and R^5 are as defined before, R^4 is ethyl and Het is pyridinyl, can also be prepared by reacting a compound of Formula (XIV) wherein R^1, R^2, R^3 and R^5 are as defined before, with hydrogen in the presence of a suitable catalyst, such as 10% palladium on charcoal, in a suitable inert solvent, such as methanol or ethanol, under suitable reaction conditions, such as a convenient temperature, typically ranging between 25 °C and 40 °C or with ammonium formate in the presence of a suitable catalyst such as 10% palladium on charcoal, in a suitable inert solvent, such as methanol, ethanol, ethyl acetate or dichloromethane or mixtures thereof, under suitable reaction conditions, such as heating at a convenient temperature, typically ranging between 40 °C and 100 °C.

Compounds of Formula (I) wherein R^1, R^2, R^3 and R^5 are as defined before, R^4 is tetrahydropyranyl and Het is pyridinyl, can also be prepared by reacting a compound of Formula (XIX)



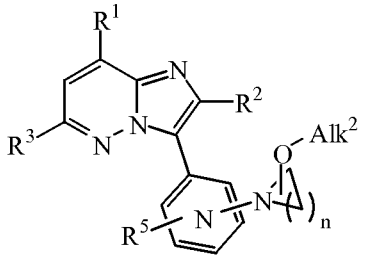
(XIX)

where R^1, R^2, R^3 and R^5 are as defined before with hydrogen in the presence of a suitable catalyst such as 10% palladium on charcoal, in a suitable inert solvent such as methanol, under suitable reaction conditions, such as a convenient temperature, typically ranging between 25 °C and 40 °C or with ammonium formate in the presence of a suitable catalyst such as 10% palladium on charcoal, in a suitable inert solvent, such as methanol, ethanol, ethyl acetate or dichloromethane or mixtures thereof, under suitable reaction conditions, such as heating at a convenient temperature, typically ranging between 40 °C and 100 °C.

A compound of Formula (XIX) wherein R^1, R^2, R^3 and R^5 are as defined before, can be prepared by reacting a compound of Formula (XV) wherein R^1, R^2, R^3 and R^5 are as defined before, with 3,6-dihydro-*2H*-pyran-4-boronic acid pinacol ester, in the presence of a suitable catalyst, such as tetrakis(triphenylphosphine)palladium (0), in the presence of a suitable base, such as sodium carbonate, in a suitable inert solvent, such as a mixture of 1,4-dioxane and water, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

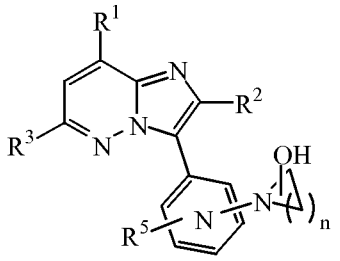
3,6-Dihydro-*2H*-pyran-4-boronic acid pinacol ester can be obtained as described before.

A compound of Formula (Id)



(Id)

wherein R^1, R^2, R^3, R^5 are as defined before, R^4 is a radical of Formula (a), n is as defined before and Alk^2 is C_{1-4}alkyl, can be prepared by reacting a compound of Formula (XX)



(XX)

where R^1, R^2, R^3, R^5 and n are as defined before with a reagent of Formula Alk^2-W wherein Alk^2 is C_{1-4}alkyl and W represents a leaving group, such as halo, e.g. chloro, bromo or iodo, in the presence of a base, such as sodium *tert*-butoxide, in the presence of a suitable crown ether, such as 18-crown-6, in a suitable solvent, such as tetrahydrofuran and under suitable reaction conditions, such as heating at a convenient temperature, typically ranging from 25 °C to 80 °C.

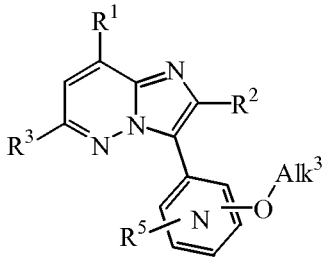
A reagent of Formula Alk^2-W where Alk^2 is C_{1-4}alkyl and W represents a leaving group, such as halo, e.g. chloro, bromo or iodo can be obtained commercially.

Compounds of Formula (I) wherein R^1, R^2, R^3, R^5 are as defined before and R^4 is $NR^{6a}R^{7a}$ and compounds of formula (XX), as previously defined, can also be prepared by reacting a compound of Formula (XV) wherein R^1, R^2, R^3 and R^5 are as defined before and the chlorine atom is *ortho* to the pyridinyl nitrogen, with a reagent of Formula $R^{6a}R^{7a}NH$, where R^{6a} and R^{7a} are as defined before, either neat or in a suitable inert solvent, such as acetonitrile, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

Alternatively, compounds of Formula (I) wherein R^1, R^2, R^3, R^5 are as defined before and R^4 is $NR^{6a}R^{7a}$, can also be prepared by reacting a compound of Formula (XV) where R^1, R^2, R^3 and R^5 are as defined before with a reagent of Formula $R^{6a}R^{7a}NH$, where R^{6a} and R^{7a} are as defined before, in the presence of a suitable catalyst, such as palladium (II) acetate, in the presence of a suitable phosphine ligand, such as racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and in the presence of a suitable base, such as cesium carbonate, in a suitable inert solvent, such as toluene, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

A reagent of Formula $R^{6a}R^{7a}NH$, where R^{6a} and R^{7a} are as defined before, can be obtained commercially.

Compounds of Formula (Ie)



(Ie)

wherein R^1, R^2, R^3 and R^5 are as defined before, R^4 is Alk^3oxy and Alk^3 is C_{1-4}alkyl, trifluoromethylC_{0-4}alkyl, C_{3-8}cycloalkylC_{1-4}alkyl, or C_{1-4}alkyloxyC_{1-5}alkyl, can be prepared by reacting a compound of Formula (XV) where R^1, R^2, R^3 and R^5 are as

defined before and the chlorine atom is *ortho* to the pyridinyl nitrogen, with a reagent of Formula Alk^3-OH, where Alk^3 is C_{1-4}alkyl, trifluoromethylC_{0-4}alkyl, C_{3-8}cycloalkylC_{1-4}alkyl, or C_{1-4}alkyloxyC_{1-5}alkyl in the presence of a suitable base, such as sodium hydride, in a suitable inert solvent such as *N*,*N*-dimethylformamide or dimethyl sulfoxide, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

A reagent of Formula Alk^3-OH wherein C_{1-4}alkyl, trifluoromethylC_{0-4}alkyl, C_{3-8}cycloalkylC_{1-4}alkyl or C_{1-4}alkyloxyC_{1-5}alkyl can be obtained commercially or can be prepared by procedures similar to those described in Morel, P. US 2008102028 A1.

Compounds of Formula (I) wherein R^1, R^2, R^3 and R^5 are as defined before, R^4 is C_{1-6}alkyl and Het is pyridinyl, can also be prepared by reacting a compound of Formula (XV) where R^1, R^2, R^3 and R^5 are as defined before and the chlorine atom is *ortho* to the pyridinyl nitrogen with a Grignard reagent of Formula R^4Mghalo, where R^4 is C_{1-6}alkyl and halo represents a chloro, bromo or iodo, in the presence of a suitable catalyst, such as [1,3-bis(diphenylphosphino)propane]dichloronickel (II) or iron (III) acetylacetonate, in a suitable inert solvent, such as a tetrahydrofuran or *N*-methylpyrrolidinone, under suitable reaction conditions, such as a convenient temperature, typically ranging between -10°C and 15°C.

A Grignard reagent of Formula R^4Mghalo where R^4 is C_{1-6}alkyl and halo is chloro, bromo or iodo, can be obtained commercially.

Alternatively, compounds of Formula (I) wherein R^1, R^2, R^3 and R^5 are as defined before and R^4 is C_{1-4}alkyl or C_{3-8}cycloalkyl and Het is pyridinyl can also be prepared by reacting a compound of Formula (XV) where R^1, R^2, R^3 and R^5 are as defined before with a boronic acid derivative of Formula $R^4B(OH)_2$, where R^4 is C_{1-4}alkyl or C_{3-8}cycloalkyl, in the presence of a suitable catalyst, such as palladium (II) acetate, in the presence of a suitable phosphine ligand, such as 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, in the presence of a suitable base, such as potassium phosphate, in a suitable inert solvent, such as toluene, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

A boronic acid derivative of Formula $R^4B(OH)_2$ where R^4 is C_{1-4}alkyl or C_{3-8}cycloalkyl can be obtained commercially.

Compounds of Formula (I) wherein R^1, R^2, R^3 and R^5 are as defined before and R^4 is C_{1-4}alkyl, C_{1-4}alkyloxyC_{1-5}alkyl or trifluoromethylC_{0-4}alkyl and Het is pyridinyl, can also be prepared by reacting a compound of Formula (XV) where R^1, R^2, R^3 and R^5 are as defined before and the chlorine atom is *ortho* to the pyridinyl nitrogen with an organozinc reagent of Formula $Zn(R^4)_2$ where R^4 represents a C_{1-4}alkyl, C_{1-4}alkyloxyC_{1-5}alkyl or trifluoromethylC_{0-4}alkyl, in the presence of a suitable catalyst, such as tetrakis(triphenylphosphine)palladium (0), in a suitable inert solvent, such as tetrahydrofuran, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

A reagent of Formula $Zn(R^4)_2$ wherein R^4 represents C_{1-4}alkyl, C_{1-4}alkyloxyC_{1-5}alkyl or trifluoromethylC_{0-4}alkyl can be obtained commercially. Alternatively, a reagent of Formula $Zn(R^4)_2$ wherein R^4 represents C_{1-4}alkyl, C_{1-4}alkyloxyC_{1-5}alkyl or trifluoromethylC_{0-4}alkyl, can be prepared by reacting a compound of Formula R^4-halo wherein R^4 represents C_{1-4}alkyl, C_{1-4}alkyloxyC_{1-5}alkyl or trifluoromethylC_{0-4}alkyl and halo represents iodo, with zinc in the presence of 1,2-dibromoethane and chlorotrimethylsilane, in a suitable inert solvent, such as *N*,*N*-dimethylformamide, under suitable reaction conditions such as heating at a convenient temperature, typically ranging between 25 °C and 100 °C.

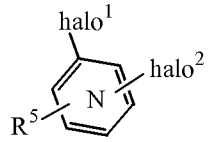
A reagent of R^4-halo wherein R^4 represents C_{1-4}alkyl, C_{1-4}alkyloxyC_{1-5}alkyl or trifluoromethylC_{0-4}alkyl and halo represents iodo can be obtained commercially or can be prepared by reacting a compound of Formula halo-R^4 wherein R^4 represents C_{1-4}alkyl, C_{1-4}alkyloxyC_{1-5}alkyl or trifluoromethylC_{0-4}alkyl and halo represents a chloro or bromo with sodium iodide in a suitable inert solvent, such as acetone, under suitable reaction conditions such as a convenient temperature, typically ranging between 25 °C and 40 °C.

A compound of Formula halo-R^4 wherein R^4 represents C_{1-4}alkyl, C_{1-4}alkyloxyC_{1-5}alkyl or trifluoromethylC_{0-4}alkyl and halo represents a chloro or bromo, can be obtained commercially.

A boronic acid of Formula (III) wherein R^4 and R^5 are as defined before, can be obtained commercially. Alternatively, a boronic acid of Formula (III) wherein R^4 and R^5 are as defined before, can be prepared by reacting a halopyridine of Formula (VI), wherein R^4 and R^5 are as defined before and halo is bromo or iodo, with triisopropyl borate, in the presence of a suitable base, such as *n*-butyllithium, in a suitable inert solvent, such as tetrahydrofuran, under suitable reaction conditions, such as a convenient temperature, typically ranging between -78°C and -10°C.

A boronic derivative of Formula (IV) wherein R^4 and R^5 are as defined before, can be obtained commercially. Alternatively, a compound of Formula (IV) wherein R^4 and R^5 are as defined before, can also be prepared by reacting a halopyridine of Formula (VI), wherein R^4 and R^5 are as defined before and halo represents a bromo or iodo, with bis(pinacolato)diboron in the presence of a suitable catalyst, such as [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II), in the presence of a suitable base, such as potassium acetate, in a suitable inert solvent, such as *N,N*-dimethylformamide or dimethyl sulfoxide, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

A halopyridine of Formula (VI) wherein R^4 and R^5 are as defined before and halo represents a bromo or iodo, can be obtained commercially. Alternatively, a halopyridine of Formula (VI) wherein R^5 is as defined before, halo represents a bromo and R^4 is C_{1-6}alkyl or C_{3-8}cycloalkyl can be prepared by reacting a di-halopyridine of Formula (XXI)



(XXI)

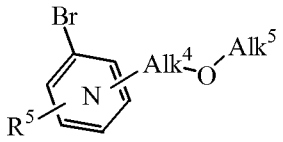
where R^5 is as defined before, $halo^1$ represent a bromo and $halo^2$ represent a bromo or iodo ortho to the pyridinyl nitrogen, with a reagent of Formula $R^4B(OH)_2$ where R^4 represents a C_{1-4}alkyl or C_{3-8}cycloalkyl, in the presence of a suitable catalyst, such as tetrakis(triphenylphosphine)palladium(0), in a suitable inert solvent, such as tetrahydrofuran, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

A boronic acid derivative of Formula $R^4B(OH)_2$ where R^4 is C_{1-4}alkyl or C_{3-8}cycloalkyl can be obtained commercially.

Alternatively, a halopyridine of Formula (VI) wherein R^5 is as defined before, halo represents a bromo an R^4 is C_{1-4}alkyl, C_{1-4}alkyloxyC_{1-5}alkyl or trifluoromethylC_{0-4}alkyl can be prepared by reacting a di-halopyridine of Formula (XXI) where R^5 is as defined before and $halo^1$ and $halo^2$ represent independently a bromo or iodo and $halo^2$ is ortho to the pyridinyl nitrogen, with an organozinc reagent of Formula $Zn(R^4)_2$ where R^4 represents a C_{1-4}alkyl, C_{1-4}alkyloxyC_{1-5}alkyl or trifluoromethylC_{0-4}alkyl, in the presence of a suitable catalyst, such as tetrakis(triphenylphosphine)palladium (0), in a suitable inert solvent, such as tetrahydrofuran, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

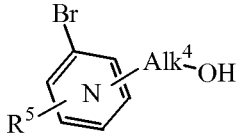
A reagent of Formula $Zn(R^4)_2$ wherein R^4 represents C_{1-4}alkyl, C_{1-4}alkyloxyC_{1-5}alkyl or trifluoromethylC_{0-4}alkyl can be obtained as described before.

Compounds of Formula (VIa)



(VIa)

wherein R^5 is as defined before, Alk^4 represents a C_{1-4}alkyl and Alk^5 represents a C_{1-4}alkyl, can be prepared by reacting a compound of Formula (VIb)



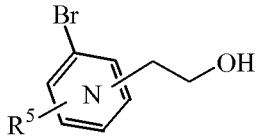
(VIb)

wherein R^5 is as defined beforeand Alk^4 represents a C_{1-4}alkyl, with a reagent of Formula $Alk^5{}_2SO_4$ where Alk^5 represents a C_{1-4}alkyl, in the presence of a suitable base, such as sodium hydride, in a suitable inert solvent, such as tetrahydrofuran, under suitable reaction conditions, such as a convenient temperature, typically ranging between -10 °C and 40 °C or with a reagent of Formula Alk^5-W wherein Alk^5 represents a C_{1-4}alkyl and W represents a leaving group, such as halo, e.g. chloro, bromo or iodo, or a sulfonyloxy group, e.g. methylsulfonyloxy, trifluoromethylsulfonyloxy, or methylphenylsulfonyloxy, in the presence of a base,

such as sodium hydride or sodium *tert*-butoxide, in the presence of a suitable crown ether, such as 18-crown-6, in a suitable solvent, such as tetrahydrofuran and under suitable reaction conditions, such as a convenient temperature, typically ranging from 0 °C to 40 °C.

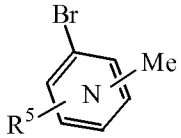
Reagents of Formula $Alk^5{}_2SO_4$ and Alk^5-W wherein Alk^5 represents a C_{1-4}alkyl and W represents a leaving group, such as halo, e.g. chloro, bromo or iodo, or a sulfonyloxy group, e.g. methylsulfonyloxy, trifluoromethylsulfonyloxy, or methylphenylsulfonyloxy, can be obtained commercially.

A compound of Formula (VIc)



(VIc)

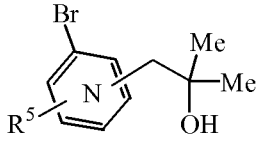
wherein R^5 is as defined before, can be prepared by reacting a methylpyridine of Formula (VId)



(VId)

wherein R^5 is as defined before and the methyl group is *ortho* to the pyridinyl nitrogen with *N*,*N*-dimethylformamide in the presence of a suitable base, such as lithium diisopropylamide, in a suitable inert solvent, such as tetrahydrofuran, under suitable reaction conditions, such as a convenient temperature, typically ranging between -78 °C and -10 °C, followed by treatment with sodium borohydride in a suitable solvent, such as methanol, under suitable reaction conditions, such as a convenient temperature, typically ranging between -10 °C and 40 °C.

A compound of Formula (VIe)



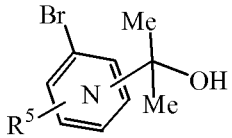
(VIe)

wherein R^5 is as defined before, can be prepared by reacting a methylpyridine of Formula (VId), wherein R^5 is as defined before and the methyl group is *ortho* to the

pyridinyl nitrogen with acetone in the presence of a suitable base, such as lithium diisopropylamide, in a suitable inert solvent, such as tetrahydrofuran, under suitable reaction conditions, such as a convenient temperature, typically ranging between -78 °C and -10 °C.

A methylpyridine of Formula (VId) wherein R^5 is as defined before, can be obtained commercially.

A compound of Formula (VIf)

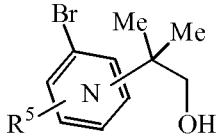


(VIf)

wherein R^5 is as defined before, can be prepared by reacting a di-halopyridine of Formula (XXI) where R^5 is as defined before, halo^1 represents a bromo and halo^2 represents a bromo *ortho* to the pyridinyl nitrogen, with acetone, in the presence of a suitable base, such as *n*-buthyllithium, in a suitable inert solvent, such as toluene, under suitable reaction conditions, such as a convenient temperature, typically ranging between -78 °C and 25 °C.

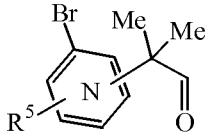
A di-halopyridine of Formula (XXI) where R^5 is as defined before, halo^1 is a bromo and halo^2 represents bromo can be obtained commercially.

A compound of Formula (VIg)



(VIg)

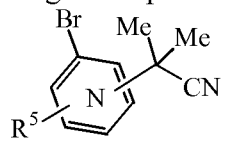
wherein R^5 is as defined before, can be prepared by reacting a compound of Formula (XXII)



(XXII)

wherein R^5 is as defined before, with sodium borohydride, in a suitable inert solvent, such as dichloromethane, under suitable reaction conditions, such as a convenient temperature, typically ranging between -10 °C and 40 °C.

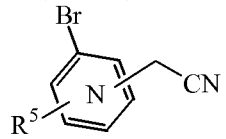
A compound of Formula (XXII) wherein R^5 is as defined before and halo represents bromo, can be prepared by reacting a compound of Formula (XXIII)



(XXIII)

wherein R^5 is as defined before, with diisobutylaluminium hydride, in a suitable inert solvent, such as dichloromethane, under suitable reaction conditions, such as a convenient temperature, typically ranging between -10 °C and 40 °C.

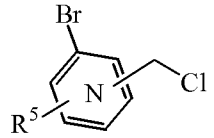
A compound of Formula (XXIII) wherein R^5 is as defined before, can be prepared by reacting a compound of Formula (XXIV)



(XXIV)

wherein R^5 is as defined before, with a suitable alkylating reagent such as iodomethane, in the presence of a base, such as sodium *tert*-butoxide, in the presence of a suitable crown ether, such as 18-crown-6, in a suitable solvent, such as tetrahydrofuran and under suitable reaction conditions, such as a convenient temperature, typically ranging between 0 °C and 40 °C.

A compound of Formula (XXIV) wherein R^5 is as defined before, can be obtained commercially or alternatively, can also be obtained by reacting a compound of Formula (XXV)

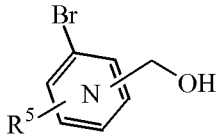


(XXV)

wherein R^5 is as defined before, with potassium cyanide, in the presence of a suitable inorganic salt, such as potassium iodide, in a suitable solvent, such as a mixture of

ethanol and water and under suitable reaction conditions, such as heating at a convenient temperature, typically ranging from 25 °C to 100 °C.

A compound of Formula (XXV) wherein R^5 is as defined before, can be obtained commercially or alternatively, can also be obtained by reacting a compound Formula (XXVI)

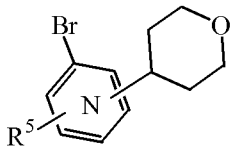


(XXVI)

wherein R^5 is as defined before, with thionyl chloride, in a suitable solvent, such as dichoromethane and under suitable reaction conditions, such as a convenient temperature, typically ranging from -10 °C to 25 °C.

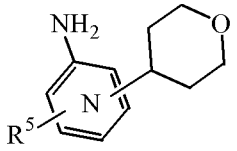
A compound of Formula (XXVI) wherein R^5 is as defined before can be obtained commercially.

Compounds of Formula (VIh)



(VIh)

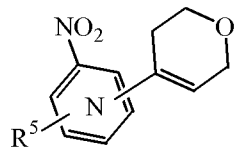
wherein R^5 is as defined before, can be prepared by reacting an amino pyridine of Formula (XXVII)



(XXVII)

where R^5 is as defined before, with sodium nitrite in the presence of a suitable inorganic salt, such as copper (I) bromide and a suitable inorganic acid, such as hydrobromic acid, in a suitable inert solvent, such as water, under suitable reaction conditions, such as a convenient temperature, typically ranging between -10 °C and 25 °C.

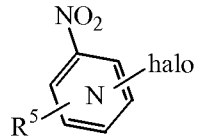
An aminopyridine of Formula (XXVII) where R^5 is as defined before, can be prepared by reacting a nitropyridine of Formula (XXVIII)



(XXVIII)

where R^5 is as defined before, with hydrogen in the presence of a suitable catalyst, such as 10% palladium on charcoal, in a suitable inert solvent, such as methanol or ethanol, under suitable reaction conditions, such as heating at a convenient temperature, typically ranging between 25 °C and 40 °C.

A nitropyridine of Formula (XXVIII) where R^5 is as defined before, can be prepared by reacting an halonitropyridine of Formula (XXIX)



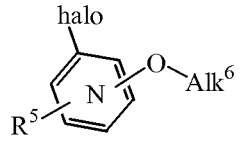
(XXIX)

where R^5 is as defined before and halo represents a chloro, bromo or iodo, with 3,6-dihydro-*2H*-pyran-4-boronic acid pinacol ester in the presence of a suitable catalyst, such as tetrakis(triphenylphosphine)palladium(0), in the presence of a suitable base, such as sodium carbonate, in a suitable inert solvent, such as a mixture of 1,4-dioxane and water, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

A halonitropyridine of Formula (XXIX) where R^5 is as defined before and halo represents a chloro, bromo or iodo can be obtained commercially.

3,6-Dihydro-*2H*-pyran-4-boronic acid pinacol ester can be obtained as described before.

Compounds of Formula (VIi)



(VIi)

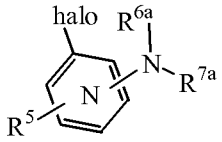
wherein R^5 is as defined before and Alk^6 is C_{1-4}alkyl, C_{1-4}alkyloxyC_{1-5}alkyl or C_{3-8}cycloalkylC_{1-4}alkyl and halo is a bromo or iodo, can be prepared by reacting a di-

halopyridine of Formula (XVIII) where R^5 is as defined before, halo represents a bromo or iodo and the chlorine atom is *ortho* to the pyridinyl nitrogen with a reagent of Formula Alk^6-OH, where Alk^6 is C_{1-4}alkyl, C_{1-4}alkyloxyC_{1-5}alkyl or C_{3-8}cycloalkylC_{1-4}alkyl in the presence of a suitable base, such as sodium hydride, in a suitable inert solvent, such as *N*,*N*-dimethylformamide or dimethyl sulfoxide, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

A di-halo pyridine of Formula (XVIII) where R^5 is as defined before, halo represents a bromo or iodo, can be obtained commercially.

A reagent of Formula Alk^6-OH wherein Alk^6 is C_{1-4}alkyl, C_{1-4}alkyloxyC_{1-5}alkyl or C_{3-8}cycloalkylC_{1-4}alkyl, can be obtained commercially or alternatively can also be obtained by procedures similar to those described in Morel, P. US 2008102028 A1.

Compounds of Formula (VIj)



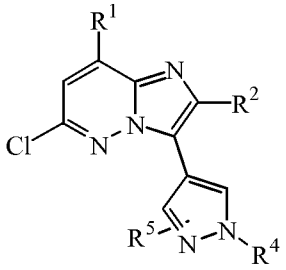
(VIj)

wherein R^5, R^{6a} and R^{7a} are as defined before and halo represents bromo or iodo, can also be prepared by reacting a di-halo pyridine of Formula (XVIII) where R^5 is as defined before, and halo represents a bromo or iodo and the chlorine atom is *ortho* to the pyridinyl nitrogen with a compound of formula $R^{6a}R^{7a}NH$, wherein R^{6a} and R^{7a} are as defined before, either neat or in a suitable inert solvent, such as acetonitrile, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

A reagent of Formula $R^{6a}R^{7a}NH$, wherein R^{6a} and R^{7a} are as defined before, can be obtained commercially.

A di-halo pyridine of Formula (XVIII) where R^5 is as defined before, halo represents a bromo or iodo, can be obtained commercially.

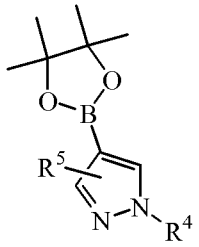
A compound of Formula (I) wherein R^1, R^2, R^4 and R^5 are as defined before, R^3 is hydrogen, Het is pyrazolyl and R^4 is attached to the nitrogen atom of the pyrazole can be prepared by reacting a compound of Formula (If)



(If)

wherein R^1, R^2, R^4 and R^5 are as defined before, with hydrogen in the presence of a suitable catalyst, such as 10% palladium on charcoal, in a suitable inert solvent, such as methanol or ethanol, under suitable reaction conditions, such as a convenient temperature, typically ranging between 25 °C and 40 °C or with ammonium formate in the presence of a suitable catalyst such as 10% palladium on charcoal, in a suitable inert solvent, such as methanol, ethanol, ethyl acetate or dichloromethane or mixtures thereof, under suitable reaction conditions, such as heating at a convenient temperature, typically ranging between 40 °C and 100 °C.

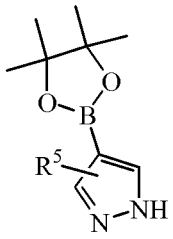
Compounds of Formula (I) wherein R^1, R^2, R^3, R^4 and R^5 are as defined before, Het is pyrazolyl and R^4 is attached to the nitrogen atom of the pyrazole can be prepared by reacting a compound of Formula (II) where R^1, R^2 and R^3 are as defined before and halo represents a bromo or iodo, with a boronate of Formula (XXX)



(XXX)

where R^4 and R^5 are as defined before, in the presence of a suitable catalyst, such as tetrakis(triphenylphosphine)palladium (0), in the presence of a suitable base, such as sodium carbonate, in a suitable inert solvent such as a mixture of 1,4-dioxane and water, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

A compound of Formula (XXX) wherein R^4 and R^5 are as defined before and R^4 is attached to the nitrogen atom of the pyrazole, can be obtained commercially or alternatively, can be prepared by reacting a compound of Formula (XXXI)



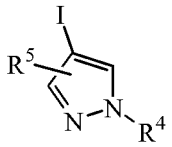
(XXXI)

wherein R^5 is as defined before, with a reagent of Formula R^4-W wherein R^4 is as defined before and W represents a leaving group, such as halo, e.g. chloro, bromo or iodo, or a sulfonyloxy group, e.g. methylsulfonyloxy, trifluoromethylsulfonyloxy, or methylphenylsulfonyloxy in the presence of a base such as cesium carbonate or diisopropylethylamine, in a suitable solvent, such as *N*,*N*-dimethylformamide or acetonitrile and under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

Compounds of Formula R^4-W wherein R^4 is as defined before and W represents a leaving group, such as halo, e.g. chloro, bromo or iodo, can be obtained commercially. Compounds of formula R^4-W wherein R^4 is as defined before and W represents a leaving group, such as a sulfonyloxy group, e.g. methylsulfonyloxy, trifluoromethylsulfonyloxy, or methylphenylsulfonyloxy can be prepared by reacting a compound of Formula R^4-OH with a sulfonyl chloride, e.g. methylsulfonyl chloride, trifluoromethylsulfonyl chloride, or methylphenylsulfonyl chloride in the presence of a suitable base, such as pyridine or diisopropylethylamine, in a suitable solvent, such as dichloromethane and under suitable reaction conditions, such as a convenient temperature, typically ranging from -10 °C to 25 °C.

Compounds of Formula R^4-OH wherein R^4 is as defined before, can be obtained commercially.

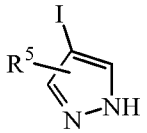
Compounds of Formula (XXX) wherein R^4 and R^5 are as defined before and R^4 is attached to the nitrogen atom of the pyrazole, can also be prepared by reacting a compound of Formula (XXXII)



(XXXII)

wherein R^4 and R^5 are as defined before, with bis(pinacolato)diboron in the presence of a suitable catalyst, such as [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II), in the presence of a suitable base, such as potassium acetate, in a suitable inert solvent, such as *N,N*-dimethylformamide or dimethyl sulfoxide, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

Compounds of Formula (XXXII) wherein R^4 and R^5 are as defined before and R^4 is attached to the nitrogen atom of the pyrazole, can be prepared by reacting a 4-iodo-*1H*-pyrazole of Formula (XXXIII)



(XXXIII)

wherein R^5 is as defined before, with a reagent of Formula R^4-W wherein R^4 is as defined before and W represents a leaving group such as halo, e.g. chloro, bromo or iodo, or a sulfonyloxy group, e.g. methylsulfonyloxy, trifluoromethylsulfonyloxy, or methylphenylsulfonyloxy in the presence of a suitable base, such as cesium carbonate or diisopropylethylamine, in a suitable solvent, such as *N,N*-dimethylformamide or acetonitrile and under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

A 4-iodo-*1H*-pyrazole of Formula (XXXIII) where R^5 is as defined before, can be obtained commercially.

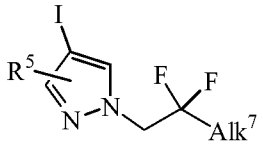
Compounds of Formula R^4-W wherein R^4 is as defined before and W represents a leaving group such as halo, e.g. chloro, bromo or iodo, can be obtained commercially.

Alternatively, compounds of formula R^4-W wherein R^4 is as defined before and W represents a leaving group such as a sulfonyloxy group, e.g. methylsulfonyloxy, trifluoromethylsulfonyloxy, or methylphenylsulfonyloxy can be prepared by reacting a

compound of formula R^4-OH with a sulfonyl chloride, e.g. methylsulfonyl chloride, trifluoromethylsulfonyl chloride, or methylphenylsulfonyl chloride in the presence of a suitable base such, as pyridine or diisopropylethylamine, in a suitable solvent, such as dichloromethane and under suitable reaction conditions, such as a convenient temperature, typically ranging from –10 °C to 25 °C.

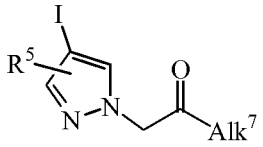
Compounds of Formula R^4-OH wherein R^4 is as defined before, can be obtained commercially.

A compound of Formula (XXXIIa)



(XXXIIa)

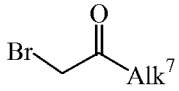
wherein R^5 is as defined before and Alk^7 represents C_{1-4}alkyl or C_{3-8}cycloalkyl groups can be prepared by reacting a compound of Formula (XXXIIb).



(XXXIIb)

wherein R^5 is as defined before and Alk^7 represents C_{1-4}alkyl or C_{3-8}cycloalkyl groups with (diethylamino)sulphur trifluoride in a suitable inert solvent, such as dichloromethane, and under suitable reaction conditions, such as convenient temperatures, typically ranging from 0 °C to 25 °C.

A compound of Formula (XXXIIb), wherein Alk^7 represents a C_{1-4}alkyl or C_{3-8}cycloalkyl group can be prepared by reacting a 4-iodo-*1H*-pyrazole of Formula (XXXIII) with an alpha bromoketone of Formula (XXXV)

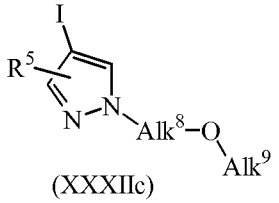


(XXXV)

wherein Alk^7 represents a C_{1-4}alkyl or aC_{3-8}cycloalkyl group, in the presence of a suitable base, such as cesium carbonate, in a suitable inert solvent, such as acetonitrile, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

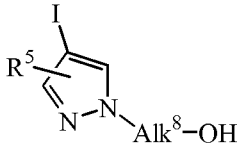
An alpha bromoketone of Formula (XXXV) wherein Alk^7 is C_{1-4}alkyl or C_{3-8}cycloalkyl, can be obtained commercially or alternatively can be obtained by procedures similar to those described in Carverley, M.J. Tetrahedron, 1987, 43(20), 4609-19.

A compound of Formula (XXXIIc)



(XXXIIc)

wherein R^5 is as defined before, Alk^8 represents C_{1-4}alkyl and Alk^9 represents C_{1-4}alkyl, can be prepared by reacting a compound of Formula (XXXVI)



(XXXVI)

where R^5 is as defined before and Alk^8 represents C_{1-4}alkyl with a reagent of Formula Alk^9-W wherein Alk^9 is C_{1-4}alkyl, and W represents a leaving group such as halo, e.g. chloro, bromo or iodo, or a sulfonyloxy group, e.g. methylsulfonyloxy, trifluoromethylsulfonyloxy, or methylphenylsulfonyloxy, in the presence of a suitable base, such as sodium hydride, in a suitable solvent such as tetrahydrofuran and under suitable reaction conditions, such as a convenient temperature, typically ranging from 0 °C to 40 °C.

A reagent of Formula Alk^9-W wherein Alk^9 is C_{1-4}alkyl and W represents a leaving group such as halo, e.g. chloro, bromo or iodo, or a sulfonyloxy group, e.g. methylsulfonyloxy, trifluoromethylsulfonyloxy, or methylphenylsulfonyloxy, can be obtained commercially.

A compound of Formula (XXXVI) wherein R^5 is as defined before, can be prepared by reacting a 4-iodo-*1H*-pyrazole of Formula (XXXIII)
where R^5 is as defined before, with a reagent of Formula W-Alk^8-OH, wherein W represents a leaving group such as halo, e.g. chloro, bromo or iodo, or a sulfonyloxy group, e.g. methylsulfonyloxy, trifluoromethylsulfonyloxy, or methylphenylsulfonyloxy and Alk^8 represents a C_{1-4}alkyl, in the presence of a suitable

base, such as cesium carbonate, in a suitable inert solvent, such as *N*,*N*-dimethylformamide, under suitable reaction conditions, such as heating at a convenient temperature, either by conventional heating or under microwave irradiation for a period of time to ensure the completion of the reaction.

A reagent of Formula W-Alk^8-OH wherein W represents a leaving group such as halo, e.g. chloro, bromo or iodo, or a sulfonyloxy group, e.g. methylsulfonyloxy, trifluoromethylsulfonyloxy, or methylphenylsulfonyloxy and Alk^8 represents C_{1-4}alkyl or C_{3-8}cycloalkyl, can be obtained commercially.

In order to obtain the acid addition salt forms of the compounds according to the invention, for example the HCl salt forms unless otherwise described, several procedures known to those skilled in the art can be used. In a typical procedure, for example, the free base can be dissolved in isopropanol, diisopropylether, diethyl ether and/or dichloromethane and subsequently, 1 to 2 equivalents of the appropriate acid, for example a 6N HCl solution in 2-propanol or a 2N HCl solution in diethyl ether, can be added dropwise. The mixture typically is stirred for 10 min or longer after which the product can be filtered off. The HCl salt is usually dried *in vacuo*.

It will be appreciated by those skilled in the art that in the processes described above the functional groups of intermediate compounds may need to be blocked by protecting groups. In case the functional groups of intermediate compounds were blocked by protecting groups, they can be deprotected after a reaction step.

Pharmacology

The compounds according to the invention inhibit PDE10 enzyme activity, in particular PDE10A enzyme activity and hence raise the levels of cAMP or cGMP within cells that express PDE10. Accordingly, inhibition of PDE10 enzyme activity may be useful in the treatment of diseases caused by deficient amounts of cAMP or cGMP in cells. PDE10 inhibitors may also be of benefit in cases in which raising the amount of cAMP or cGMP above normal levels results in a therapeutic effect. Inhibitors of PDE10 may be used to treat disorders of the peripheral and central nervous system, cardiovascular diseases, cancer, gastro-enterological diseases, endocrinological or metabolic diseases and urological diseases.

Hence, the present invention relates to a compound according to the present invention for use as a medicine, as well as to the use of a compound according to the invention or

a pharmaceutical composition according to the invention for the manufacture of a medicament. The present invention also relates to a compound according to the present invention or a pharmaceutical composition according to the invention for use in the treatment or prevention of, in particular treatment of, a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the inhibition of phosphodiesterase 10 enzyme. The present invention also relates to the use of a compound according to the present invention or a pharmaceutical composition according to the invention for the manufacture of a medicament for the treatment or prevention of, in particular treatment of, a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the inhibition of phosphodiesterase 10 enzyme.

The present invention also relates to a compound according to the invention, or a pharmaceutical composition according to the invention for use in the treatment, prevention, amelioration, control or reduction of the risk of various neurological, psychiatric and metabolic disorders associated with phosphodiesterase 10 dysfunction in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the inhibition of phosphodiesterase 10.

Also, the present invention relates to the use of a compound according to the invention or a pharmaceutical composition according to the invention for the manufacture of a medicament for treating, preventing, ameliorating, controlling or reducing the risk of various neurological and psychiatric disorders associated with phosphodiesterase 10 dysfunction in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the inhibition of phosphodiesterase 10.

Where the invention is said to relate to the use of a compound or composition according to the invention for the manufacture of a medicament for e.g. the treatment of a mammal, it is understood that such use is to be interpreted in certain jurisdictions as a method of e.g. treatment of a mammal, comprising administering to a mammal in need of such e.g. treatment, an effective amount of a compound or composition according to the invention.

In particular, the indications that may be treated with PDE10 inhibitors, either alone or in combination with other drugs, include, but are not limited to, those diseases thought to be mediated in part by the basal ganglia, prefrontal cortex and hippocampus.

These indications include neurological and psychiatric disorders selected from psychotic disorders and conditions; anxiety disorders; movement disorders; drug abuse; mood disorders; neurodegenerative disorders; disorders or conditions comprising as a symptom a deficiency in attention and/or cognition; pain and metabolic disorders.

In particular, the psychotic disorders and conditions associated with PDE10 dysfunction include one or more of the following conditions or diseases: schizophrenia, for example of the paranoid, disorganized, catatonic, undifferentiated or residual type; schizophreniform disorder; schizoaffective disorder, such as delusional or depressive type; delusional disorder; substance-induced psychotic disorder such as psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, inhalants, opioids, or phencyclidine; personality disorders of the paranoid type; and personality disorder of the schizoid type.

In particular, the anxiety disorders include panic disorder; agoraphobia; specific phobia; social phobia; obsessive-compulsive disorder; post-traumatic stress disorder; acute stress disorder; and generalized anxiety disorder.

In particular, movement disorders include Huntington's disease and dyskinesia; Parkinson's disease; restless leg syndrome and essential tremor. Additionally, Tourette's syndrome and other tic disorders can be included.

In particular, the central nervous system disorder is a substance-related disorder selected from the group of alcohol abuse; alcohol dependence; alcohol withdrawal; alcohol withdrawal delirium; alcohol-induced psychotic disorder; amphetamine dependence; amphetamine withdrawal; cocaine dependence; cocaine withdrawal; nicotine dependence; nicotine withdrawal; opioid dependence and opioid withdrawal.

In particular, mood disorders and mood episodes include depression, mania and bipolar disorders. Preferably, the mood disorder is selected from the group of bipolar disorders (I and II); cyclothymic disorder; depression; dysthymic disorder; major depressive disorder and substance-induced mood disorder.

In particular, neurodegenerative disorders include Parkinson's disease; Huntington's disease; dementia such as for example Alzheimer's disease; multi-infarct dementia; AIDS-related dementia or fronto temperal dementia. The neurodegenerative disorder or condition comprises neurodegeneration of striatal medium spiny neurons.

In particular, disorders or conditions comprising as a symptom a deficiency in attention and/or cognition include dementia, such as Alzheimer's disease; multi-infarct dementia; alcoholic dementia or drug-related dementia; dementia associated with intracranial tumours or cerebral trauma; dementia associated with Huntington's disease; dementia associated with Parkinson's disease; AIDS-related dementia; other diseases include delirium; amnestic disorder; post-traumatic stress disorder; mental retardation; a learning disorder; attention-deficit/hyperactivity disorder (ADHD); and age-related cognitive impairment.

In particular, pain includes acute and chronic states, severe pain, intractable pain, neuropathic pain and post-traumatic pain.

In particular, metabolic disorders include diabetes, in particular type 1 or type 2 diabetes, and related disorders such as obesity. Additional related disorders include syndrome X, impaired glucose tolerance, impaired fasting glucose, gestational diabetes, maturity-onset diabetes of the young (MODY), latent autoimmune diabetes adult (LADA), associated diabetic dyslipidemia, hyperglycemia, hyperinsulinemia, dyslipidemia, hypertriglyceridemia, and insulin resistance.

Additionally, the growth of some cancer cells is inhibited by cAMP and cGMP, the compounds of the invention may be useful in the treatment of cancer, such as renal carcinoma and breast cancer.

Preferably, the psychotic disorder is selected from the group of schizophrenia, delusional disorder, schizoaffective disorder, schizophreniform disorder and substance-induced psychotic disorder.

Preferably, the central nervous system disorder is a personality disorder selected from the group of obsessive-compulsive personality disorder and schizoid, schizotypal disorder.

Preferably, the central nervous system disorder is a mood disorder selected from the group of bipolar disorders (I & II), cyclothymic disorder, depression, dysthymic disorder, major depressive disorder and substance-induced mood disorder.

Preferably, the central nervous system disorder is attention-deficit/hyperactivity disorder.

Preferably, the central nervous system disorder is a cognitive disorder selected from the group of delirium, substance-induced persisting delirium, dementia, dementia due to HIV disease, dementia due to Huntington's disease, dementia due to Parkinson's disease, dementia of the Alzheimer's type, substance-induced persisting dementia and mild cognitive impairment.

Preferably the disorders treated by the compounds of the present invention are selected from schizophrenia; obsessive-compulsive disorder; generalized anxiety disorder; Huntington's disease; dyskinesia; Parkinson's disease; depression; bipolar disorders; dementia such as Alzheimer's disease; attention-deficit/hyperactivity disorder; drug abuse; pain; diabetes and obesity.

Preferably, the disorders treated by the compounds of the present invention are schizophrenia, including positive and negative symptoms thereof, and cognitive deficits, such as impaired attention or memory.

Of the disorders mentioned above, the treatment of anxiety, obsessive-compulsive disorder, schizophrenia, depression, attention-deficit/hyperactivity disorder, Alzheimer's disease and diabetes are of particular importance.

At present, the fourth edition of the Diagnostic & Statistical Manual of Mental Disorders (DSM-IV) of the American Psychiatric Association provides a diagnostic tool for the identification of the disorders described herein. The person skilled in the art will recognize that alternative nomenclatures, nosologies, and classification systems for neurological and psychiatric disorders described herein exist, and that these evolve with medical and scientific progresses.

Therefore, the invention also relates to a compound according to the invention, for use in the treatment of any one of the diseases mentioned hereinbefore.

The invention also relates to a compound according to the invention for use in treating any one of the diseases mentioned hereinbefore.

The invention also relates to a compound according to the invention, for the treatment or prevention, in particular treatment, of any one of the diseases mentioned hereinbefore.

The invention also relates to the use of a compound according to the invention, for the manufacture of a medicament for the treatment or prevention of any one of the disease conditions mentioned hereinbefore.

The invention also relates to the use of a compound according to the invention for the manufacture of a medicament for the treatment of any one of the disease conditions mentioned hereinbefore.

The compounds of the present invention can be administered to mammals, preferably humans, for the treatment or prevention of any one of the diseases mentioned hereinbefore.

In view of the utility of the compounds according to the invention, there is provided a method of treating warm-blooded animals, including humans, suffering from any one of the diseases mentioned hereinbefore, and a method of preventing in warm-blooded animals, including humans, any one of the diseases mentioned hereinbefore.

Said methods comprise the administration, i.e. the systemic or topical administration, preferably oral administration, of a therapeutically effective amount of a compound according to the invention to warm-blooded animals, including humans.

Therefore, the invention also relates to a method for the prevention and/or treatment of any one of the diseases mentioned hereinbefore comprising administering a therapeutically effective amount of compound according to the invention to a patient in need thereof.

The PDE10 inhibitors described herein can be used alone, in combination or in combination with other pharmaceutical agents such as other agents used in the treatment of psychoses, such as schizophrenia and bipolar disorder, obsessive-

compulsive disorder, Parkinson's disease, cognitive impairment and/or memory loss, e.g. nicotinic α-7 agonists, PDE4 inhibitors, other PDE10 inhibitors, calcium channel blockers, muscarinic m1 and m2 modulators, adenosine receptor modulators, ampakines, NMDA-R modulators, mGluR modulators, dopamine modulators, serotonin modulators, cannabinoid modulators, and cholinesterase inhibitors (e.g. donepezil, rivastigmine, and galantamine). In such combinations, the compounds of the present invention may be utilized in combination with one or more other drugs in the treatment, prevention, control, amelioration, or reduction of risk of diseases or conditions for which compounds of Formula (I) or the other drugs may have utility, where the combination of the drugs together are safer or more effective than either drug alone.

One skilled in the art will recognize that a therapeutically effective amount of the PDE10 inhibitors of the present invention is the amount sufficient to inhibit the PDE10 enzyme and that this amount varies *inter alia*, depending on the type of disease, the concentration of the compound in the therapeutic formulation, and the condition of the patient. Generally, an amount of PDE10 inhibitor to be administered as a therapeutic agent for treating diseases in which inhibition of the PDE10 enzyme is beneficial, such as the disorders described herein, will be determined on a case by case by an attending physician.

Generally, a suitable dose is one that results in a concentration of the PDE10 inhibitor at the treatment site in the range of 0.5 nM to 200 μM, and more usually 5 nM to 50 μM. To obtain these treatment concentrations, a patient in need of treatment likely will be administered between 0.001 mg/kg to 15 mg/kg body weight, in particular from 0.01 mg/kg to 2.50 mg/kg body weight, in particular, from 0.01 to 1.5 mg/kg body weight, in particular from 0.1 mg/kg to 0.50 mg/kg body weight. The amount of a compound according to the present invention, also referred to here as the active ingredient, which is required to achieve a therapeutical effect will, of course vary on case-by-case basis, vary with the particular compound, the route of administration, the age and condition of the recipient, and the particular disorder or disease being treated. A method of treatment may also include administering the active ingredient on a regimen of between one and four intakes per day. In these methods of treatment the compounds according to the invention are preferably formulated prior to admission. As described herein below, suitable pharmaceutical formulations are prepared by known procedures using well known and readily available ingredients.

Pharmaceutical compositions

The present invention also provides compositions for preventing or treating diseases in which inhibition of the PDE10 enzyme is beneficial, such as the disorders

described herein. While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical composition. Accordingly, the present invention also relates to a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and, as active ingredient, a therapeutically effective amount of a compound according to the invention, in particular a compound according to Formula (I), a pharmaceutically acceptable salt thereof, a solvate thereof or a stereochemically isomeric form thereof. The carrier or diluent must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipients thereof.

The compounds according to the invention, in particular the compounds according to Formula (I), the pharmaceutically acceptable salts thereof, the solvates and the stereochemically isomeric forms thereof, or any subgroup or combination thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs.

The pharmaceutical compositions of this invention may be prepared by any methods well known in the art of pharmacy, for example, using methods such as those described in Gennaro et al. Remington's Pharmaceutical Sciences (18^{th} ed., Mack Publishing Company, 1990, see especially Part 8: Pharmaceutical preparations and their Manufacture). To prepare the pharmaceutical compositions of this invention, a therapeutically effective amount of the particular compound, optionally in salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier or diluent, which carrier or diluent may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, in particular, for oral, topical (for example via a nose spray, eye drops or via a cream, gel, shampoo or the like), rectal or percutaneous administration, by parenteral injection or by inhalation, such as a nose spray. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as, for example, suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as, for example, starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of the ease in administration, oral administration is preferred, and tablets and capsules represent the most advantageous oral dosage unit forms in which case solid pharmaceutical carriers are employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, surfactants to aid

solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, said additives do not introduce a significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on treatment, as an ointment.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, teaspoonfuls, tablespoonfuls, and segregated multiples thereof.

Since the compounds according to the invention are orally administrable compounds, pharmaceutical compositions comprising aid compounds for oral administration are especially advantageous.

In order to enhance the solubility and/or the stability of the compounds of Formula (I) in pharmaceutical compositions, it can be advantageous to employ α-, β- or γ-cyclodextrins or their derivatives, in particular hydroxyalkyl substituted cyclodextrins, e.g. 2-hydroxypropyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin. Also co-solvents such as alcohols may improve the solubility and/or the stability of the compounds according to the invention in pharmaceutical compositions.

The exact dosage and frequency of administration depends on the particular compound of formula (I) used, the particular condition being treated, the severity of the condition being treated, the age, weight, sex, extent of disorder and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the

treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention.

Depending on the mode of administration, the pharmaceutical composition will comprise from 0.05 to 99 % by weight, preferably from 0.1 to 70 % by weight, more preferably from 0.1 to 50 % by weight of the active ingredient, and, from 1 to 99.95 % by weight, preferably from 30 to 99.9 % by weight, more preferably from 50 to 99.9 % by weight of a pharmaceutically acceptable carrier, all percentages being based on the total weight of the composition.

The amount of a compound of Formula (I) that can be combined with a carrier material to produce a single dosage form will vary depending upon the disease treated, the mammalian species, and the particular mode of administration. However, as a general guide, suitable unit doses for the compounds of the present invention can, for example, preferably contain between 0.1 mg to about 1000 mg of the active compound. A preferred unit dose is between 1 mg to about 500 mg. A more preferred unit dose is between 1 mg to about 300mg. Even more preferred unit dose is between 1 mg to about 100 mg. Such unit doses can be administered more than once a day, for example, 2, 3, 4, 5 or 6 times a day, but preferably 1 or 2 times per day, so that the total dosage for a 70 kg adult is in the range of 0.001 to about 15 mg per kg weight of subject per administration. A preferred dosage is 0.01 to about 1.5 mg per kg weight of subject per administration, and such therapy can extend for a number of weeks or months, and in some cases, years. It will be understood, however, that the specific dose level for any particular patient will depend on a variety of factors including the activity of the specific compound employed; the age, body weight, general health, sex and diet of the individual being treated; the time and route of administration; the rate of excretion; other drugs that have previously been administered; and the severity of the particular disease undergoing therapy, as is well understood by those of skill in the area.

A typical dosage can be one 1 mg to about 100 mg tablet or 1 mg to about 300 mg taken once a day, or, multiple times per day, or one time-release capsule or tablet taken once a day and containing a proportionally higher content of active ingredient. The time-release effect can be obtained by capsule materials that dissolve at different pH values, by capsules that release slowly by osmotic pressure, or by any other known means of controlled release.

It can be necessary to use dosages outside these ranges in some cases as will be apparent to those skilled in the art. Further, it is noted that the clinician or treating physician will know how and when to start, interrupt, adjust, or terminate therapy in conjunction with individual patient response.

As already mentioned, the invention also relates to a pharmaceutical composition comprising the compounds according to the invention and one or more other drugs for use as a medicament or for use in the treatment, prevention, control, amelioration, or reduction of risk of diseases or conditions for which compounds of Formula (I) or the other drugs may have utility as well. The use of such a composition for the manufacture of a medicament, as well as the use of such a composition for the manufacture of a medicament in the treatment, prevention, control, amelioration or reduction of risk of diseases or conditions for which compounds of Formula (I) or the other drugs may have utility are also contemplated. The present invention also relates to a combination of a compound according to the present invention and an additional pharmaceutical agent. The present invention also relates to such a combination for use as a medicine. The present invention also relates to a product comprising (a) a compound according to the present invention, a pharmaceutically acceptable salt thereof or a solvate thereof, and (b) an additional pharmaceutical agent, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the effect of PDE10 inhibitors, in particular PDE10A inhibitors. The different drugs of such a combination or product may be combined in a single preparation together with pharmaceutically acceptable carriers or diluents, or they may each be present in a separate preparation together with pharmaceutically acceptable carriers or diluents.

The following examples are intended to illustrate but not to limit the scope of the present invention.

Examples

Chemistry

Several methods for preparing the compounds of this invention are illustrated in the following Examples. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification.

Hereinafter, the term "LCMS" means liquid chromatography/mass spectrometry, "HPLC" means high-performance liquid chromatography, "min." means minutes, "h." means hours, "R_t" means retention time (in minutes), "$[M+H]^+$" means the protonated mass of the free base of the compound, "m.p." means melting point.

Microwave assisted reactions were performed in a single-mode reactor: Emrys™ Optimizer microwave reactor (Personal Chemistry A.B., currently Biotage).

Thin layer chromatography (TLC) was carried out on silica gel 60 F254 plates (Merck) using reagent grade solvents. Open column chromatography was performed on silica gel, particle size 60 Å, mesh = 230-400 (Merck) under standard techniques. Flash column chromatography was performed using ready-to-connect cartridges from Merck, on irregular silica gel, particle size 15-40 μm (normal phase disposable flash columns) on an SPOT or FLASH system from Armen Instrument.

Reverse phase HPLC was performed on a C18 XBridge 30 x 100 5 μm column.

^{1}H NMR spectra were recorded either on a Bruker DPX-400 or on a Bruker AV-500 spectrometer with standard pulse sequences, operating at 400 MHz and 500 MHz respectively. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), which was used as internal standard.

Melting Point values are peak values, and are obtained with experimental uncertainties that are commonly associated with this analytical method. For a number of compounds, melting points were determined in open capillary tubes either on a Mettler FP62 or on a Mettler FP81HT-FP90 apparatus. Melting points were measured with a temperature gradient of 10 °C/minute. Maximum temperature was 300 °C. The melting point was read from a digital display.

LCMS analysis

General procedure for HP 1100-MS instruments (TOF, SQD or MSD)

The HPLC measurement was performed using an HP 1100 (Agilent Technologies) system comprising a pump (quaternary or binary) with degasser, an autosampler, a column oven, a diode-array detector (DAD) and a column as specified in the respective methods. The MS detector was configured with either an electrospray ionization source or an ESCI dual ionization source (electrospray combined with atmospheric pressure chemical ionization). Nitrogen was used as the nebulizer gas. The source temperature was maintained either at 140 °C or 100°C. Data acquisition was performed either with MassLynx-Openlynx software or Chemsation-Agilent Data Browser software.

General procedure for Acquity-SQD instrument

The UPLC (Ultra Performance Liquid Chromatography) measurement was performed using an Acquity UPLC (Waters) system comprising a sampler organizer, a binary pump with degasser, a four column's oven, a diode-array detector (DAD) and a column as specified in the respective methods. The MS detector was configured with an ESCI dual ionization source (electrospray combined with atmospheric pressure chemical ionization). Nitrogen was used as the nebulizer gas. The source temperature was maintained at 140 °C. Data acquisition was performed with MassLynx-Openlynx software.

MS Procedure for LC Method 1: High-resolution mass spectra (Time of Flight, TOF detector) were acquired only in positive ionization mode or in positive/negative modes by scanning from 100 to 750 umas. The capillary needle voltage was 2.5 kV for positive mode and 2.9kV for negative ionization mode. The cone voltage was 20 V for both positive and negative ionization modes. Leucine-Enkephaline was the standard substance used for the lock mass calibration.

MS Procedure for LC Methods 2, 4, 5, and 6: Low-resolution mass spectra (single quadrupole, SQD detector) were acquired only in positive ionization mode or in positive/negative modes by scanning from 100 to 1000 umas. The capillary needle voltage was 3 kV. For positive ionization mode the cone voltage was 20 V, 25 V or 20 V/50 V. For negative ionization mode the cone voltage was 30 V.

MS Procedure for LC Method 3

Low-resolution mass spectra (single quadrupole, MSD detector) were acquired in positive/negative modes by scanning from 100 to 1000 umas. The capillary needle voltage was 1.0 kV and the fragmentor voltage was 70V for both positive and negative ionization modes.

Method 1

In addition to the general procedure: Reversed phase HPLC was carried out on a Sunfire-C18 column (2.5 μm, 2.1 x 30 mm) from Waters, with a flow rate of 1.0 ml/min, at 60 °C. The gradient conditions used are: 95% A (0.5 g/L ammonium acetate solution + 5% of acetonitrile), 5% B (acetonitrile or or acetonitrile/methanol 1/1), to 100% B and equilibrated to initial conditions up to 7 or 9 minutes run. Injection volume 2 μL.

Method 2

In addition to the general procedure: Reversed phase HPLC was carried out on an Eclipse Plus-C18 column (3.5 µm, 2.1 x 30 mm) from Agilent, with a flow rate of 1.0 mL/min, at 60 °C. The gradient conditions used are: 95% A (0.5 g/L ammonium acetate solution + 5% acetonitrile), 5% B (acetonitrile or mixture of acetonitrile / methanol, 1/1), to 100% B and equilibrated to initial conditions up to 7 or 9 minutes run. Injection volume 2 µL.

Method 3

In addition to the general procedure: Reversed phase HPLC was carried out on an Eclipse Plus-C18 column (3.5 µm, 2.1 x 30 mm) from Agilent, with a flow rate of 1.0 mL/min, at 60 °C. The gradient conditions used are: 95% A (0.5 g/L ammonium acetate solution + 5% acetonitrile), 5% B (acetonitrile), to 100% B in 5.0 minutes, kept till 5.15 minutes and equilibrated to initial conditions at 5.3 minutes until 7.0 minutes. Injection volume 2 µL.

Method 4

In addition to the general procedure: Reversed phase UPLC was carried out on a BEH-C18 column (1.7 µm, 2.1 x 50 mm) from Waters, with a flow rate of 0.8 mL/min, at 60 °C. The gradient conditions used are: 95% A (0.5 g/L ammonium acetate solution + 5% acetonitrile), 5% B (mixture of acetonitrile / methanol, 1/1), to 20% A, 80 % B, then to 100% B and equilibrated to initial conditions up to 5 or 7 minutes run. Injection volume 0.5 µL.

Method 5

In addition to the general procedure: Reversed phase UPLC was carried out on a BEH-C18 column (1.7 µm, 2.1 x 50 mm) from Waters, with a flow rate of 1.0 mL/min, at 50°C. The gradient conditions used are: 95% A (0.5 g/L ammonium acetate solution + 5% acetonitrile), 5% B (acetonitrile), to 40% A, 60 % B, then to 5% A, 95% B and equilibrated to initial conditions up to 5, 7, or 9 minutes run. Injection volume 0.5 µL.

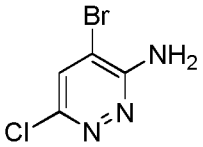
Method 6

In addition to the general procedure: Reversed phase UPLC was carried out on a BEH-C18 column (1.7 µm, 2.1 x 50 mm) from Waters, with a flow rate of 0.8 mL/min, at 50°C. The gradient conditions used are: 95% A (formic acid solution, 0.1%), 5% B (methanol), to 40% A, 60 % B, then to 5% A, 95% B and equilibrated to initial conditions up to 7.0 minutes run. Injection volume 0.5 µL.

A. Preparation of the intermediates

Example A1

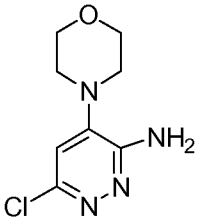
Preparation of intermediate 1: 4-Bromo-6-chloro-pyridazin-3-ylamine



Bromine (7.9 ml, 154.3 mmol) was added to a stirred suspension of 6-chloro-pyridazin-3-ylamine (20 g, 154.3 mmol) and sodium hydrogencarbonate (25.9 g, 308.8 mol) in methanol (500 ml). The mixture was stirred at room temperature for 16 h, then filtered. The filtrate was diluted with ethyl acetate and washed with a saturated solution of sodium thiosulfate, water and a saturated solution of sodium carbonate. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo* to yield **intermediate 1** (24.59 g, 64%) as a brown solid which was used in next step without further purification. LCMS: 208 $[M+H]^+$; R_t: 0.59 min (method 5).

Example A2

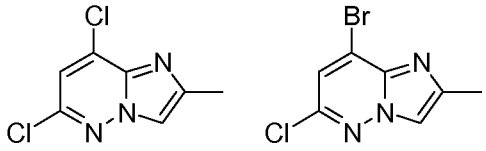
Preparation of intermediate 2: 6-Chloro-4-morpholin-4-yl-pyridazin-3-ylamine



Morpholine (8.37 ml, 95.9 mmol) was added to a stirred solution of **intermediate 1** (2 g, 9.6 mmol) in acetonitrile (5 ml). The mixture was stirred at 80 °C for 16 h., then diluted with dichloromethane and washed with a saturated solution of sodium hydrogen carbonate. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica, methanol in dichloromethane 0/100 to 30/70). The desired fractions were collected and concentrated *in vacuo* to yield **intermediate 2** (1.98 g, 92%) as a pale brown solid. LCMS: 215 $[M+H]^+$; R_t: 0.56 min (method 5).

Example A3

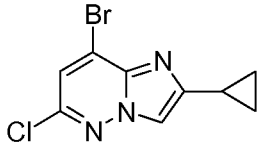
Preparation of intermediate 3: Mixture of 6,8-dichloro-2-methyl-imidazo[1,2-*b*]pyridazine and 8-bromo-6-chloro-2-methyl-imidazo[1,2-*b*]pyridazine



A mixture of **intermediate 1** (28.57 g, 137.1 mmol) and chloroacetone (76.4 ml, 959.4 mmol) was stirred at 90°C for 16 h. in a sealed tube protected from light. After cooling to room temperature, diethylether was added and the solid formed was filtered off and washed with further diethylether. The solid was suspended in a saturated solution of sodium carbonate and extracted with dichloromethane. The organic layer was dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude products were purified by open column chromatography (silica; dichloromethane). The desired fractions were collected and concentrated *in vacuo* to yield **intermediate 3** (19.5 g, 66%) as a white solid, in a 70/30 mixture of 6,8-dichloro-2-methyl-imidazo[1,2-*b*]pyridazine and 8-bromo-6-chloro-2-methyl-imidazo[1,2-*b*]pyridazine. $C_7H_5Cl_2N_3$ requires 201; Found 202 $[M+H]^+$; R_t: 1.25 min and $C_7H_5BrClN_3$ requires 247; Found 248 $[M+H]^+$; R_t: 1.33 min (method 5).

Example A4

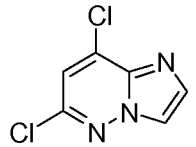
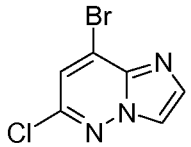
Preparation of intermediate 4: 8-Bromo-6-cloro-2-cyclopropyl-imidazo[1,2-*b*]pyridazine



A mixture of **intermediate 1** (5 g, 24 mmol) and 2-bromo-1-cyclopropyl-ethanone (15.25 g, 93.6 mmol) (obtained by a procedure similar to those described in Gaudry, M.; Marquet, A. Organic Syntheses 1976, 55) was stirred at 80 °C for 16 h. The crude product was suspended in dichloromethane and washed with a saturated solution of sodium hydrogen carbonate. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; dichloromethane in heptane 40/60 to 100/0). The desired fractions were collected and concentrated *in vacuo* to yield **intermediate 4** (4.95 g, 76%) as a black solid. $C_9H_7BrClN_3$ requires 271; Found 272 $[M+H]^+$. R_t: 2.05 min (method 5).

Example A5

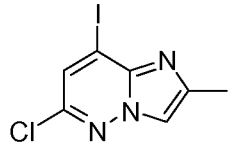
Preparation of intermediate 5: Mixture of 6,8-dichloro-imidazo[1,2-*b*]pyridazine and 8-bromo-6-chloro-imidazo[1,2-*b*]pyridazine

A 50% wt. solution of chloroacetaldehyde in water (5.79 ml, 44.5 mmol) was added dropwise to a solution of **intermediate 1** (2.34 g, 11.2 mmol) in ethanol (50 ml). The mixture was stirred at reflux temperature for 2 h. After cooling to room temperature, the mixture was poured onto a mixture of ice / water and ethyl acetate was added. The mixture was basified by addition of a saturated solution of sodium carbonate. The organic layer was separated, washed with brine, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude products were purified by open column chromatography (silica; 7M solution of ammonia in methanol in dichloromethane 2/98). The desired fractions were collected and concentrated *in vacuo* to yield **intermediate 5** (1.5 g, 66%) as a 68/32 mixture of 6,8-dichloro-imidazo[1,2-*b*]pyridazine and 8-bromo-6-chloro-imidazo[1,2-*b*]pyridazine.

Example A6

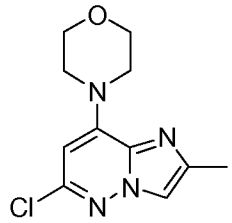
Preparation of intermediate 6: 6-Chloro-8-iodo-2-methyl-imidazo[1,2-*b*]pyridazine



Hydriodic acid (0.1 ml, 0.74 mmol) was added to a solution of **intermediate 3** (a 70/30 mixture of 6,8-dichloro-2-methyl-imidazo[1,2-*b*]pyridazine and 8-bromo-6-chloro-2-methyl-imidazo[1,2-*b*]pyridazine) (1 g, 4.95 mmol) and sodium iodide (2.23 g, 45.1 mmol) in acetonitrile (10 ml). The mixture was stirred at 160 °C for 30 min. in a sealed tube, under microwave irradiation and then poured onto a 10% w/w solution of sodium carbonate. The mixture was diluted with dichloromethane and washed with a 10% solution of sodium thiosulfite. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; ethyl acetate in heptane 0/100 to 50/50). The desired fractions were collected and concentrated *in vacuo* to yield **intermediate 6** (1.25 g, 86%) as a light brown solid. LCMS: 294 $[M+H]^+$; R_t: 1.52 min (method 5).

Example A7

Preparation of intermediate 7: 6-Chloro-2-methyl-8-morpholin-4-yl-imidazo[1,2-*b*]pyridazine

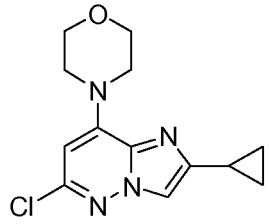


Morpholine (6.48 ml, 74.2 mmol) was added to a stirred solution of **intermediate 3** (a 70/30 mixture of 6,8-dichloro-2-methyl-imidazo[1,2-*b*]pyridazine and 8-bromo-6-chloro-2-methyl-imidazo[1,2-*b*]pyridazine) (12.5 g, 58.0 mmol) and *N*,*N*-diisopropylethylamine (16.2 ml, 92.8 mmol) in acetonitrile (40 ml). The mixture was stirred at 80 °C for 16 h. and then diluted with dichloromethane and washed with a saturated solution of ammonium chloride. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was triturated with diethylether to yield **intermediate 7** (15.4 g, 99 %) as a pale brown solid. LCMS: 253 $[M+H]^+$; R_t: 1.62 min (method 5).

The following intermediates were prepared from the indicated precursors according to a protocol analogous to **A7**.

Example A8

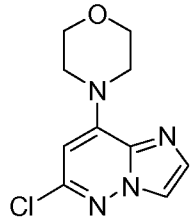
Preparation of intermediate 8: 6-Chloro-2-cyclopropyl-8-morpholin-4-yl-imidazo[1,2-*b*]pyridazine



From **intermediate 4**. Flash column chromatography (silica; ethyl acetate in heptane 30/70) yielded **intermediate 8** as a white solid (81%). LCMS: 279 $[M+H]^+$; R_t: 2.60 min (method 4).

Example A9

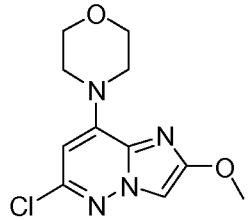
Preparation of intermediate 9: 6-Chloro-8-morpholin-4-yl-imidazo[1,2-*b*]pyridazine



From **intermediate 5** (a 68/32 mixture of 6,8-dichloro-imidazo[1,2-*b*]pyridazine and 8-bromo-6-chloro-imidazo[1,2-*b*]pyridazine). Open column chromatography (silica, dichloromethane) yielded **intermediate 9** as a pale yellow solid (66%).

Example A10

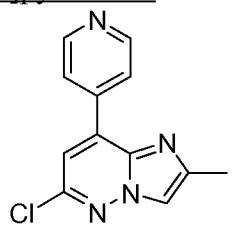
Preparation of intermediate 10: 6-Chloro-2-methoxy-8-morpholin-4-yl-imidazo[1,2-*b*]pyridazine



A mixture of **intermediate 2** (0.7 g, 3.26 mmol) and methyl bromoacetate (0.93 ml, 9.78 mmol) in methanol (2.5 ml) was stirred at 130 °C for 15 min under microwave irradiation. The mixture was diluted with water and extracted with dichloromethane. The organic layer was separated, extracted with brine, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; 7 M solution of ammonia in methanol in dichloromethane 0/100 to 3/97). The desired fractions were collected and concentrated *in vacuo* to yield **intermediate 10** (0.314 g, 29%).

Example A11

Preparation of intermediate 11: 6-Chloro-2-methyl-8-pyridin-4-yl-imidazo[1,2-*b*]pyridazine



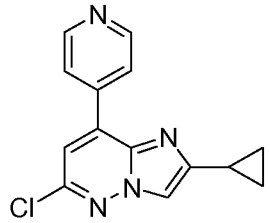
Tetrakis(triphenylphosphine)palladium (0) (0.114 g, 0.10 mmol) was added to a stirred solution of **intermediate 3** (a mixture 70/30 of 6,8-dichloro-2-methyl-imidazo[1,2-

b]pyridazine and 8-bromo-6-chloro-2-methyl-imidazo[1,2-*b*]pyridazine) (0.4 g, 2.0 mmol) and 4-pyridineboronic acid (0.243 g, 2.0 mmol) in a mixture of 1,4-dioxane (2 ml) and a saturated solution of sodium carbonate (2 ml). The mixture was stirred at 100 °C for 16 h. in a sealed tube under nitrogen and then filtered through a pad of diatomaceous earth. The filtrate was diluted with dichloromethane and extracted with a saturated solution of sodium carbonate. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by column chromatography (silica; ethyl acetate in heptane 0/100 to 50/50). The desired fractions were collected and concentrated *in vacuo* to yield **intermediate 11** (0.26 g, 41%). LCMS: 288 $[M+H]^+$; R_t: 2.17 min (method 4).

The following intermediates were prepared from the indicated precursors according to a protocol analogous to **A11**.

Example A12

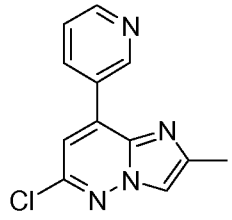
Preparation of intermediate 12: 6-Chloro-2-cyclopropyl-8-pyridin-4-yl-imidazo[1,2-*b*]pyridazine



From **intermediate 4**. Flash column chromatography (silica; ethyl acetate in dichloromethane 0/100 to 30/70) yielded **intermediate 12** as a pale yellow solid (52%). LCMS: 271 $[M+H]^+$; R_t: 2.11 min (method 5).

Example A13

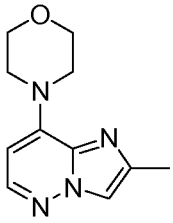
Preparation of intermediate 13: 6-Chloro-2-methyl-8-pyridin-3-yl-imidazo[1,2-*b*]pyridazine



From **intermediate 6** and 3-pyridineboronic acid. Conditions: 140 °C for 15 min under microwave irradiation. Flash column chromatography (silica; 7 M solution of ammonia in methanol in dichloromethane 0/100 to 4/96) yielded **intermediate 13** as a pale brown solid (100%).

Example A14

Preparation of intermediate 14: 2-Methyl-8-morpholin-4-yl-imidazo[1,2-*b*]pyridazine

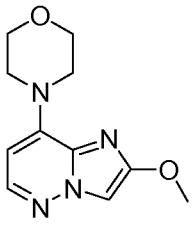


10% Palladium on charcoal (0.421 g) was added to a suspension of **intermediate 7** (1 g, 3.96 mmol) and ammonium formate (0.75 g, 11.9 mmol) in methanol (25 ml). The mixture was stirred at 80 °C for 4 h. and at room temperature for a further 16 h. The mixture was filtered through a pad of diatomaceous earth and the filtrate was concentrated *in vacuo*. The crude product was suspended in dichloromethane and washed with a saturated solution of sodium hydrogen carbonate. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo* to yield **intermediate 14** (0.78 g, 90%) as a white solid. LCMS: 219 $[M+H]^+$; R_t: 0.98 min (method 5).

The following intermediates were prepared from the indicated precursors according to a protocol analogous to **A14**.

Example A15

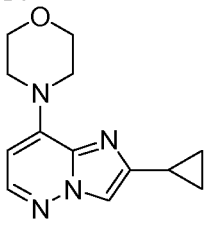
Preparation of intermediate 15: 2-Methoxy-8-morpholin-4-yl-imidazo[1,2-*b*]pyridazine



From **intermediate 10**. Flash column chromatography (7 M solution of ammonia in methanol in dichloromethane 0/100 to 3/97) yielded **intermediate 15** as a pale brown solid (65%).

Example A16

Preparation of intermediate 16: 2-Cyclopropyl-8-morpholin-4-yl-imidazo[1,2-*b*]pyridazine

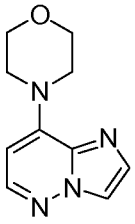


10% Palladium on charcoal (0.391 g) was added to a mixture of **intermediate 8** (4.1 g, 14.7 mmol) and triethylamine (4.1 ml, 29.4 mmol) in a mixture of methanol (100 ml) and tetrahydrofuran (100 ml). The mixture was hydrogenated (atmospheric pressure) at room temperature for 8 h and then filtered through a pad of diatomaceous earth. The filtrate was concentrated *in vacuo* to yield **intermediate 16** (3.1 g, 94%). LCMS: 219 $[M+H]^+$; R_t: 0.98 min (method 5).

The following intermediates were prepared from the indicated precursors according to a protocol analogous to **A16**.

Example A17

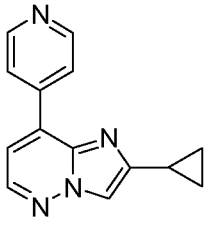
Preparation of intermediate 17: 8-Morpholin-4-yl-imidazo[1,2-*b*]pyridazine



From **intermediate 9**. Precipitation from diisopropylether yielded **intermediate 17** as a pale pink solid (76%).

Example A18

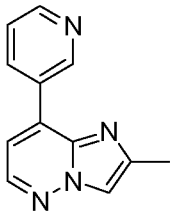
Preparation of intermediate 18: 2-Cyclopropyl-8-pyridin-4-yl-imidazo[1,2-*b*]pyridazine



From **intermediate 12**. Flash column chromatography (silica; ethylacetate in heptane 0/100 to 50/50) yielded **intermediate 18** as a white solid (50%). LCMS: 237 $[M+H]^+$; R_t: 1.83 min (method 5).

Example A19

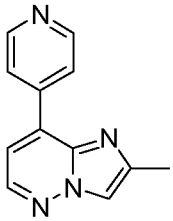
Preparation of intermediate 19: 2-Methyl-8-pyridin-3-yl-imidazo[1,2-*b*]pyridazine



From **intermediate 13**. Flash column chromatography (silica, 7 M solution of ammonia in methanol in dichloromethane 0/100 to 2/98) yielded **intermediate 19** as a pale brown solid (43%). LCMS: 211 $[M+H]^+$; R_t: 1.14 min (method 5).

Example A20

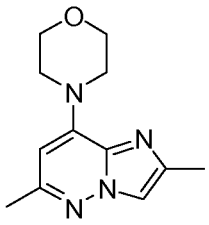
Preparation of intermediate 20: 2-Methyl-8-pyridin-4-yl-imidazo[1,2-*b*]pyridazine



10% Palladium on charcoal (1.22 g) was added to a suspension of **intermediate 11** (4 g, 16.35 mmol) in a mixture of methanol (400 ml) and dichlorometane (30 ml). The mixture was hydrogenated (40 psi) at 50 °C for 6 h. and then filtered through a pad of diatomaceous earth. The filtrate was concentrated *in vacuo* to yield **intermediate 20** (3 g, 86%) as a yellow solid. LCMS: 211 $[M+H]^+$; R_t: 2.11 min (method 1).

Example A21

Preparation of intermediate 21: 2,6-Dimethyl-8-morpholin-4-yl-imidazo[1,2-*b*]pyridazine



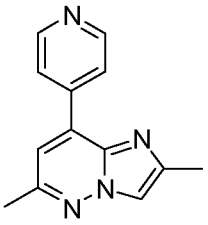
Tetrakis(triphenylphosphine)palladium (0) (0.457 g, 0.396 mmol) was added to a stirred solution of **intermediate 7** (1 g, 3.96 mmol) and methylboronic acid (1.18 g, 19.79 mmol) in a mixture of 1,4-dioxane (12 ml) and a saturated solution of sodium carbonate (4 ml). The mixture was stirred at 175 °C for 45 min. in a sealed tube under

nitrogen and under microwave irradiation. The mixture was filtered through a pad of diatomaceous earth and the filtrate diluted with ethylacetate and washed with water. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by column chromatography (silica; ethyl acetate in heptane 20/80 to 50/50). The desired fractions were collected and concentrated *in vacuo* to yield **intermediate 21** (0.364 g, 40%). LCMS: 233 $[M+H]^+$; R_t: 1.98 min (method 2).

The following intermediates were prepared from the indicated precursors according to a protocol analogous to **A21**.

Example A22

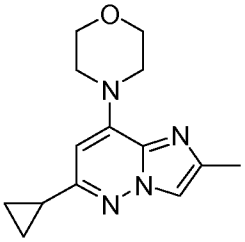
Preparation of intermediate 22: 2,6-Dimethyl-8-pyridin-4-yl-imidazo[1,2-*b*]pyridazine



From **intermediate 11**. Flash column chromatography (silica; 7 M solution of ammonia in methanol in dichloromethane 0/100 to 1.5/98.5) yielded **intermediate 22** as a light yellow solid (65%). LCMS: 225 $[M+H]^+$; R_t: 2.00 min (method 2).

Example A23

Preparation of intermediate 23: 6-Cyclopropyl-2-methyl-8-morpholin-4-yl-imidazo[1,2-*b*]pyridazine



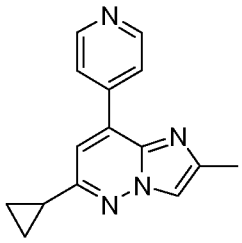
Palladium (II) acetate (0.066 g, 0.297 mmol) was added to a stirred solution of **intermediate 7** (0.5 g, 1.98 mmol), cyclopropylboronic acid (0.255 g, 2.97 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (0.244 g, 0.594 mmol) and potassium phosphate (0.84 g, 3.96 mmol) in toluene (10 ml). The mixture was stirred at 150 °C for 45 min. in a sealed tube under nitrogen and under microwave irradiation. The mixture was diluted with dichloromethane and washed with water. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude

product was purified by column chromatography (silica; ethyl acetate in heptane 0/100 to 50/50). The desired fractions were collected and concentrated *in vacuo* to yield **intermediate 23** (0.434 g, 85%). LCMS: 259 $[M+H]^+$; R_t: 2.22 min (method 5).

The following intermediates were prepared from the indicated precursors according to a protocol analogous to **A23**.

Example A24

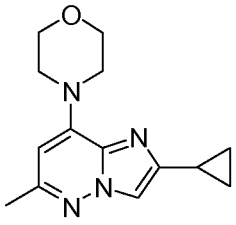
Preparation of intermediate 24: 6-Cyclopropyl-2-methyl-8-pyridin-4-yl-imidazo[1,2-*b*]pyridazine



From **intermediate 11**. Flash column chromatography (7 M solution of ammonia in methanol in dichloromethane 0/100 to 4/96) yielded **intermediate 24** as a light yellow solid (87%). LCMS: 251 $[M+H]^+$; R_t: 2.20 min (method 5).

Example A25

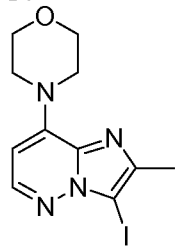
Preparation of intermediate 25: 2-Cyclopropyl-6-methyl-8-morpholin-4-yl-imidazo[1,2-*b*]pyridazine



From **intermediate 8** and methylboronic acid. Flash column chromatography (silica; ethyl acetate in dichloromethane 0/100 to 30/70) yielded **intermediate 25** as a pale yellow solid (75%).

Example A26

Preparation of intermediate 26: 3-Iodo-2-methyl-8-morpholin-4-yl-imidazo[1,2-*b*]pyridazine

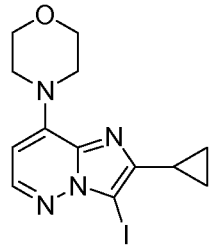


N-Iodosuccinimide (1.08 g, 4.8 mmol) was added to a stirred solution of **intermediate 14** (1 g, 4.58 mmol) in a mixture of dichloromethane (50 ml) and acetic acid (2 ml). The mixture was stirred at 0 °C for 30 min. and then extracted with a saturated solution of sodium carbonate and a 10% solution of sodium thiosulfite. The organic layer was filtered over cotton wool and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica, dichloromethane in heptane 70/30 first, then ethyl acetate in heptane 10/90 to 30/70). The desired fractions were collected and concentrated to yield **intermediate 26** (4.68 g, 83 %) as a white solid. LCMS: 345 $[M+H]^+$; R_t: 2.59 min (method 1).

The following intermediates were prepared from the indicated precursors according to a protocol analogous to **A26**.

Example A27

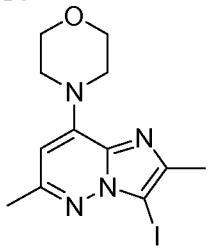
Preparation of intermediate 27: 2-Cyclopropyl-3-iodo-8-morpholin-4-yl-imidazo[1,2-*b*]pyridazine



From **intermediate 16**. Flash column chromatography (silica; ethyl acetate in dichloromethane 0/100 to 20/80) yielded **intermediate 27** as a pale brown solid (95%). LCMS: 371 $[M+H]^+$; R_t: 3.15 min (method 5).

Example A28

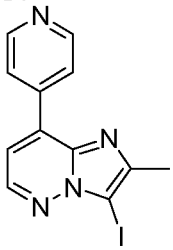
Preparation of intermediate 28: 3-Iodo-2,6-dimethyl-8-morpholin-4-yl-imidazo[1,2-*b*]pyridazine



From **intermediate 21**. Flash column chromatography (silica; 7 M solution of ammonia in methanol in dichloromethane 0/100 to 2/98) yielded **intermediate 28** as a white solid (77%). LCMS: 359 $[M+H]^+$; R_t: 2.84 min (method 2).

Example A29

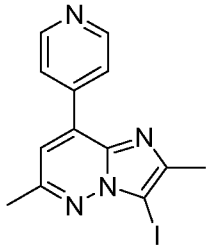
Preparation of intermediate 29: 3-Iodo-2-methyl-8-pyridin-4-yl-imidazo[1,2-*b*]pyridazine



From **intermediate 20**. Flash column chromatography (silica; ethyl acetate in dichloromethane 0/100 to 30/70) yielded **intermediate 29** as a pale yellow solid (96%). LCMS: 351 $[M+H]^+$; R_t: 2.43 min (method 2).

Example A30

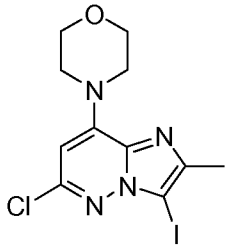
Preparation of intermediate 30: 3-Iodo-2,6-dimethyl-8-pyridin-4-yl-imidazo[1,2-*b*]pyridazine



From **intermediate 22**. Flash column chromatography (silica; ethyl acetate in dichloromethane 30/70 to 70/30) yielded **intermediate 30** as a pale yellow solid (72%). LCMS: 351 $[M+H]^+$; R_t: 2.71 min (method 2).

Example A31

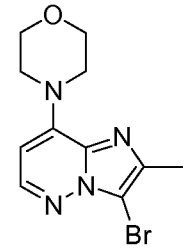
Preparation of intermediate 31: 6-Chloro-3-iodo-2-methyl-8-morpholin-1-yl-imidazo[1,2-*b*]pyridazine



N-Iodosuccinimide (0.95 g, 4.36 mmol) was added to a stirred solution of a mixture 70/30 of **intermediate 3** (0.95 g, 3.36 mmol) in a mixture of dichloromethane (9 ml) and acetic acid (1 ml). The mixture was stirred at room temperature for 16 h. and then washed with a saturated solution of sodium carbonate. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo* to yield 1.33 g of crude product. A portion of this crude product (0.5 g) was dissolved in acetonitrile (8 ml) and morpholine (0.140 ml, 1.6 mmol) and *N*,*N*-diisopropylethylamine (0.393 ml, 2.29 mmol) were added. The mixture was stirred at 150 °C for 10 min in a sealed tube, under microwave irradiation. The mixture was diluted with ethyl acetate and washed with a saturated solution of ammonium chloride. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo* to yield **intermediate 31** (0.53 g, 69%).

Example A32

Preparation of intermediate 32: 3-Bromo-2-methyl-8-morpholin-4-yl-imidazo[1,2-*b*]pyridazine



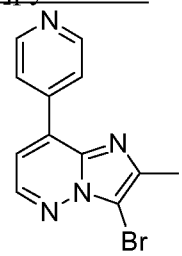
N-Bromosuccinimide (0.273 g, 1.53 mmol) was added to a stirred solution of **intermediate 14** (0.335 g, 1.53 mmol) in acetonitrile (10 ml). The mixture was stirred at room temperature for 1h., then diluted with ethyl acetate and washed with a saturated solution of sodium carbonate. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica, 7 M solution of ammonia in methanol in dichloromethane 4/96). The desired fractions were collected and concentrated *in vacuo* and the crude

product purified again by flash column chromatography (silica, ethyl acetate in heptane 0/100 to 100/0). The desired fractions were collected and concentrated *in vacuo* to yield **intermediate 32** (0.1 g, 21.2 %).

The following intermediates were prepared from the indicated precursors according to a protocol analogous to **A32**.

Example A33

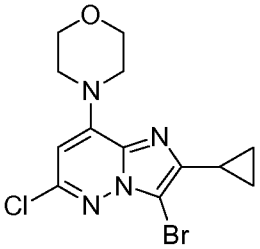
Preparation of intermediate 33: 3-Bromo-2-methyl-8-pyridin-4-yl-imidazo[1,2-*b*]pyridazine



From **intermediate 20**. Flash column chromatography (silica; 7 M solution of ammonia in methanol in dichloromethane 0/100 to 4/96) to yield **intermediate 33** as a pale brown solid (73%).

Example A34

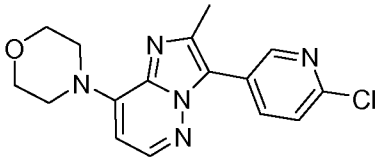
Preparation of intermediate 34: 3-Bromo-6-chloro-2-cyclopropyl-8-morpholin-4-yl-imidazo[1,2-*b*]pyridazine



From **intermediate 8**. Flash column chromatography (silica, dichloromethane) yielded **intermediate 34** as a white solid (59%). LCMS: 357 $[M+H]^+$; R_t: 3.16 min (method 4).

Example A35

Preparation of intermediate 35: 3-(6-Chloro-pyridin-3-yl)-2-methyl-8-morpholin-4-yl-imidazo[1,2-*b*]pyridazine

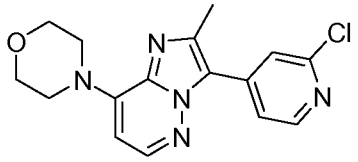


Tetrakis(triphenylphosphine)palladium (0) (0.403 g, 0.35 mmol) was added to a stirred solution of **intermediate 26** (4 g, 11.6 mmol) and 2-chloropyridine-5-boronic acid (2.01 g, 12.79 mmol) in a mixture of 1,4-dioxane (40 ml) and a saturated solution of sodium carbonate (20 ml). The mixture was stirred at 100 °C for 16 h. in a sealed tube under nitrogen and then diluted with dichloromethane and extracted with water. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was precipitated from methanol to yield **intermediate 35** (0.364 g, 40%). LCMS: 330 $[M+H]^+$; R_t: 1.90 min (method 5).

The following intermediates were prepared from the indicated precursors according to a protocol analogous to **A35**.

Example A36

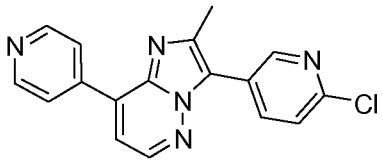
Preparation of intermediate 36: 3-(2-Chloro-pyridin-4-yl)-2-methyl-8-morpholin-4-yl-imidazo[1,2-*b*]pyridazine



From **intermediate 26** and 2-chloropyridine-4-boronic acid. Precipitation from methanol yielded **intermediate 36** as a pale brown solid (95 %).

Example A37

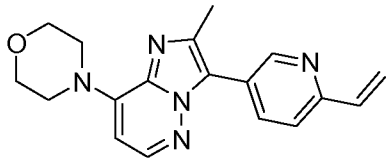
Preparation of intermediate 37: 3-(6-Chloro-pyridin-3-yl)-2-methyl-8-pyridin-4-yl-imidazo[1,2-*b*]pyridazine



From **intermediate 29**. Conditions: 150 °C for 15 min. under microwave irradiation. Precipitation from methanol yielded **intermediate 37** as a pale brown solid (71%).

Example A38

Preparation of intermediate 38: 2-Methyl-8-morpholin-4-yl-3-(6-vinyl-pyridin-3-yl)-imidazo[1,2-*b*]pyridazine

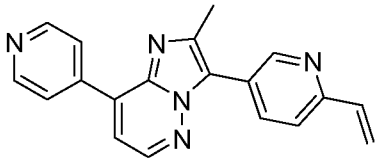


Tetrakis(triphenylphosphine)palladium (0) (0.099 g, 0.086 mmol) was added to a stirred solution of **intermediate 35** (0.945 g, 2.86 mmol) and vinylboronic acid pinacol ester (0.58 ml, 3.44 mmol) in a mixture of 1,4-dioxane (20 ml) and a saturated solution of sodium carbonate (4 ml). The mixture was stirred at 90 °C for 16 h. in a sealed tube under nitrogen. The mixture was diluted with dichloromethane and washed with water. The organic layer was separated, filtered over cotton and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; 7 M solution of ammonia in methanol in dichloromethane 0/100 to 4/96). The desired fractions were collected and concentrated *in vacuo* to yield **intermediate 38** (0.159 g, 74%). LCMS: 322 $[M+H]^+$; R_t: 3.66 min (method 6).

The following intermediate was prepared from the indicated precursors according to a protocol analogous to **A38**.

Example A39

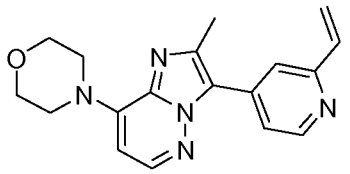
Preparation of intermediate 39: 2-Methyl-8-pyridin-4-yl-3-(6-vinyl-pyridin-3-yl)-imidazo[1,2-*b*]pyridazine



From **intermediate 37**. Conditions: 150 °C for 15 min. under microwave irradiation. Flash column chromatography (silica; ethyl acetate in dichloromethane 0/100 to 50/50) yielded **intermediate 39** as a yellow solid (100%). LCMS: 314 $[M+H]^+$; R_t: 1.67 min (method 5).

Example A40

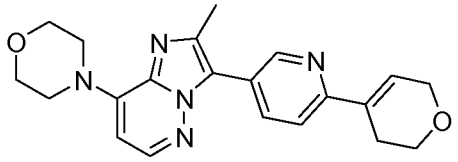
Preparation of intermediate 40: 2-Methyl-8-morpholin-4-yl-3-(2-vinyl-pyridin-4-yl)-imidazo[1,2-*b*]pyridazine



From **intermediate 36**. Conditions: 150 °C for 15 min. under microwave irradiation. Flash column chromatography (silica; ethyl acetate in heptane 20/80 to 40/60) yielded **intermediate 40** as a white solid (90%). LCMS: 322 $[M+H]^+$; R_t: 1.83 min (method 5).

Example A41

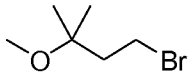
Preparation of intermediate 41: 3-[6-(3,6-Dihydro-*2H*-pyran-4-yl)-pyridin-3-yl]-2-methyl-8-morpholin-4-yl-imidazo[1,2-*b*]pyridazine



Tetrakis(triphenylphosphine)palladium (0) (0.037 g, 0.032 mmol) was added to a stirred solution of **intermediate 35** (0.35 g, 1.06 mmol) and 3,6-dihydro-*2H*-pyran-4-boronic acid pinacol ester (0.267 ml, 1.24 mmol) (obtained by procedures similar to those described in, Qiu, Y. et al. WO 2004/075846-A2 published on 20040910) in a mixture of 1,4-dioxane (5 ml) and a saturated solution of sodium carbonate (2 ml). The mixture was stirred at 85 °C for 5 h. in a sealed tube under nitrogen, then diluted with dichloromethane and washed with water. The organic layer was separated, dried ($MgSO_4$), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; ethyl acetate in heptane 20/80 to 0/100). The desired fractions were collected and concentrated *in vacuo* to yield **intermediate 41** (0.159 g, 62%).

Example A42

Preparation of intermediate 42: 1-Bromo-3-methoxy-3-methyl-butane

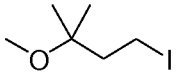


Triphenylphosphine (12.3 g, 47.0 mmol) was added to a stirred solution of 3-methoxy-3-methyl-butan-1-ol (4 ml, 31.3 mmol) and carbon tetrabromide (15.6 g, 47.0 mmol) in dichloromethane (300 ml) at 0 °C. The mixture was stirred at room temperature for 18 h. and then a solution of sodium thiosulphate was added. The organic layer was

separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was triturated with diethyl ether, filtered off and purified by flash column chromatography (silica; petroleum ether in dichloromethane 0/100 to 50/50). The desired fractions were collected and concentrated *in vacuo* to yield **intermediate 42** (2.1 g, 37%).

Example A43

Preparation of intermediate 43: 1-Iodo-3-methoxy-3-methyl-butane

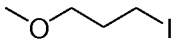


Sodium iodide (2.9 g, 19.3 mmol) was added to a stirred solution of **intermediate 42** (1.4 g, 7.7 mmol) in dry acetone (10 ml). The mixture was stirred at reflux temperature for 3 h. and then filtered. The filtrate was carefully concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica; dichloromethane). The desired fractions were collected and concentrated *in vacuo* to yield **intermediate 43** (1.7 g, 81%).

The following intermediates were prepared from the indicated precursors according to a protocol analogous to **A43**.

Example A44

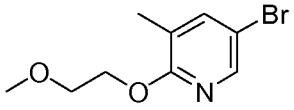
Preparation of intermediate 44: 1-Iodo-3-methoxy-propane



From 1-bromo-3-methoxy-propane. Flash column chromatography (silica; dichloromethane) yielded **intermediate 44** as a colourless oil (84%).

Example A45

Preparation of intermediate 45: 5-Bromo-2-(2-methoxy-ethoxy)-3-methyl-pyridine



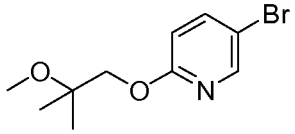
2-Methoxy-ethanol (1.18 ml, 14.95 mmol) was added dropwise to a stirred suspension of a 60% dispersion of sodium hydride in mineral oils (0.558 g, 13.95 mmol) in dimethylsulfoxide (30 ml). The mixture was stirred at room temperature for 30 min. and then 2,5-dibromo-3-methylpyridine (2.5 g, 9.96 mmol) was added. The mixture was stirred at 60 °C for 1 h. and then diluted with heptane and washed with water. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica;

dichloromethane in heptanes 70/30). The desired fractions were collected and concentrated *in vacuo* to yield **intermediate 45** (2.23 g, 91%).

The following intermediates were prepared from the indicated precursors according to a protocol analogous to **A45**.

Example A46

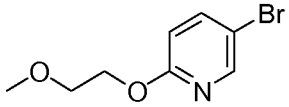
Preparation of intermediate 46: 5-Bromo-2-(2-methoxy-2-methyl-propoxy)-pyridine



From 2-methoxy-2-methyl-propan-1-ol (obtained by procedures similar to those described in, Morel, P. US 2008102028-A1 published on 20080501) and 5-bromo-2-chloro-pyridine. Flash column chromatography (silica; dichloromethane in heptane 50/50 to 70/30) yielded i**ntermediate 46** as a clear syrup (75%).

Example A47

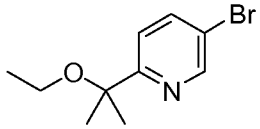
Preparation of intermediate 47: 5-Bromo-2-(2-methoxy-ethoxy)-pyridine



From 2-methoxy-ethanol and 5-bromo-2-chloro-pyridine. Flash column chromatography (silica; dichloromethane in heptane 30/70 to 70/30) yielded **intermediate 47** as a colourless oil (75%). LCMS: 232 $[M+H]^+$; R_t: 2.50 min (method 1).

Example A48

Preparation of intermediate 48: 5-Bromo-2-(1-ethoxy-1-methyl-ethyl)-pyridine



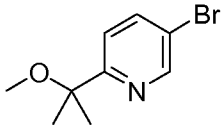
A solution of 2-(5-bromo-pyridin-2-yl)-propan-2-ol (0.80 g, 3.70 mmol) (obtained by procedures similar to those described in, Wang, X. et al. Tetrahedron Lett., 2000, 4335) in tetrahydrofuran (8 ml) was added dropwise to a stirred suspension of a 60% dispersion of sodium hydride in mineral oils (0.440 mg, 11.1 mmol) in tetrahydrofuran (6 ml). The mixture was stirred at 0 °C for 20 min. and then iodoethane (1.27 ml, 15.9 mmol) was added dropwise. The mixture was stirred at room temperature for 4 d., then diluted with dichloromethane and washed with water. The organic layer was separated,

dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; ethyl acetate in heptane 0/100 to 20/80). The desired fractions were collected and concentrated *in vacuo* to yield **intermediate 48** (0.7 g, 77%). LCMS: 244 $[M+H]^+$; R_t: 2.93 min (method 5).

The following intermediate was prepared from the indicated precursors according to a protocol analogous to **A48**.

Example A49

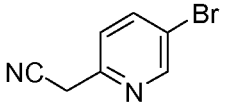
Preparation of intermediate 49: 5-Bromo-2-(1-methoxy-1-methyl-ethyl)-pyridine



From 2-(5-bromo-pyridin-2-yl)-propan-2-ol (obtained by procedures similar to those described in, Wang, X. et al.; Tetrahedron Lett., 2000, 4335) and dimethylsulfate. Flash column chromatography (silica; dichloromethane in heptane 0/100 to 50/50) yielded **intermediate 49** as a colourless oil (69%). LCMS; 230 $[M+H]^+$; R_t: 1.81 min (method 5).

Example A50

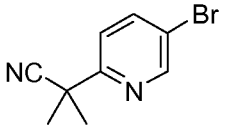
Preparation of intermediate 50: (5-Bromo-pyridin-2-yl)-acetonitrile



Potassium cyanide (0.489 g, 7.41 mmol) and potassium iodide (0.013 g, 0.079 mmol) were added to a stirred solution of 5-bromo-2-chloromethyl-pyridine (0.9 g, 3.70 mmol) (obtained by procedures similar to those described in, van den Heuvel, M. et al.; J. Org. Chem., 2004, 250) in a mixture of ethanol (6 ml) and water (2 ml). The mixture was stirred at 80 °C for 6 h., then diluted with dichloromethane and washed with a saturated solution of sodium hydrogen carbonate. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; dichloromethane). The desired fractions were collected and concentrated *in vacuo* to yield **intermediate 50** (0.498 g, 68%).

Example A51

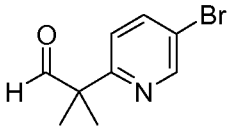
Preparation of intermediate 51: 2-(5-Bromo-pyridin-2-yl)-2-methyl-propionitrile



Iodomethane (1.14 ml, 18.27 mmol) was added to a stirred mixture of **intermediate 50** (0.45 g, 2.28 mmol), potassium *tert*-butoxide (0.64 g, 5.71 mmol) and 18-crown-6 (0.091 g, 0.34 mmol) in tetrahydrofuran (10 ml). The mixture was stirred at room temperature for 18 h., then diluted with dichloromethane and washed with water. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; dichloromethane). The desired fractions were collected and concentrated *in vacuo* to yield **intermediate 51** (0.503 g, 98%).

Example A52

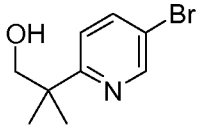
Preparation of intermediate 52: 2-(5-Bromo-pyridin-2-yl)-2-methyl-propionaldehyde



A 1 M solution of diisobutylaluminium hydride in toluene (2.46 ml, 2.46 mmol) was added to a stirred solution of **intermediate 51** (0.503 g, 2.23 mmol) in dichloromethane (5 ml) at -78 °C under nitrogen. The mixture was allowed to warm to room temperature and then stirred for 18 h. The mixture was cooled down to -78 °C and a further 1 M solution of diisobutylaluminium hydride in toluene (1 ml, 1.0 mmol) was added. The mixture was stirred at room temperature for 4 h., then a 0.5 M sulphuric acid solution was added at -78 °C, after which the reaction was diluted with dichloromethane and filtered through a pad of diatomaceous earth. The organic layer was separated, dried ($MgSO_4$), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; dichloromethane in heptane 50/50 to 100/0). The desired fractions were collected and concentrated *in vacuo* to yield **intermediate 52** (0.2 g, 40%).

Example A53

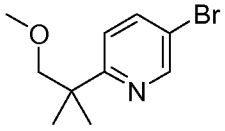
Preparation of intermediate 53: 2-(5-Bromo-pyridin-2-yl)-2-methyl-propan-1-ol



Sodium borohydride (0.043 g, 1.14 mmol) was added to a stirred solution of **intermediate 52** (0.2 mg, 0.88 mmol) in dichloromethane (5 ml). The mixture was stirred at room temperature for 2 h. and then a saturated solution of sodium hydrogen carbonate was added. The organic layer was separated, dried ($MgSO_4$), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; ethyl acetate). The desired fractions were collected and concentrated *in vacuo* to yield **intermediate 53** (0.2 g, 40%).

Example A54

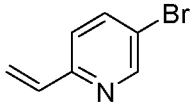
Preparation of intermediate 54: 5-Bromo-2-(2-methoxy-1,1-dimethyl-ethyl)-pyridine



Iodomethane (0.16 ml, 2.61 mmol) was added to a stirred mixture of **intermediate 53** (0.20 g, 0.87 mmol), potassium *tert*-butoxide (0.146 mg, 1.30 mmol) and 18-crown-6 (0.34 mg, 0.13 mmol) in tetrahydrofuran (5 ml). The mixture was stirred at room temperature for 18 h., then diluted with dichloromethane and washed with water. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; dichloromethane). The desired fractions were collected and concentrated *in vacuo* to yield **intermediate 54** (0.088 mg, 41 %).

Example A55

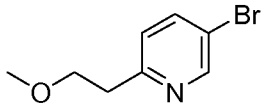
Preparation of intermediate 55: 5-Bromo-2-vinyl-pyridine



Tetrakis(triphenylphosphine)palladium(0) (1.82 g, 1.53 mmol) was added to a stirred suspension of 2,5-dibromopyridine (15 g, 63.3 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (11.8 ml, 69.6 mmol) in a mixture of 1,4-dioxane (120 ml) and a saturated solution of sodium carbonate (36 ml). The mixture was stirred at 100 °C for 16 h. in a sealed tube under nitrogen. The mixture was diluted with dichloromethane and washed with water. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; dichloromethane in heptane 20/80 to 80/20). The desired fractions were collected and concentrated *in vacuo* to yield **intermediate 55** (6.23 g, 53 %). LCMS: 184 $[M+H]^+$; R_t: 2.47 min (method 3).

Example A56

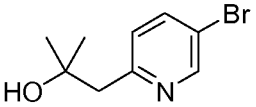
Preparation of intermediate 56: 5-Bromo-2-(2-methoxyethyl)-pyridine



Sodium methoxide (5.48 g, 101.6 mmol) was added to a solution of **intermediate 55** (6.23 g, 33.8 mmol) in dry methanol (120 ml). The mixture was stirred at 90 °C for 36 h. and then further sodium methoxide (1.82 g, 33.8 mmol) was added. The mixture was stirred at 90 °C for 7 h. and the solvents evaporated *in vacuo*. The crude product was dissolved in dichloromethane and washed with water. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; heptane in dichloromethane 70/30 to 0/100). The desired fractions were collected and concentrated *in vacuo* to yield **intermediate 56** (3.78 g, 52%). LCMS: 216 $[M+H]^+$; R_t: 1.21 min (method 5).

Example A57

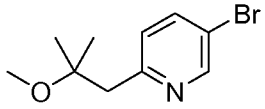
Preparation of intermediate 57: 1-(5-Bromo-pyridin-2-yl)-2-methyl-propan-2-ol



A 2.5 M solution of *n*-butyllithium in pentane (8.37 ml, 20.9 mmol) was added dropwise to a stirred solution of *N,N*-diisopropylamine (3.45 ml, 24.4 mmol) in dry tetrahydrofuran (20 ml) at -78 °C. The mixture was stirred at 0 °C for 30 min, cooled down to -78 °C. and then added dropwise to a solution of 5-bromo-2-picoline (3.0 g, 17.4 mmol) in tetrahydrofuran (20 ml). The mixture was stirred at -78 °C for 15 min. and then acetone (3.85 ml, 52.3 mmol) was added dropwise. The mixture was stirred at -78 °C for 20 min. and then a saturated solution of ammonium chloride was added. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; ethyl acetate in dichloromethane 0/100 to 20/80). The desired fractions were collected and concentrated *in vacuo* to yield **intermediate 57** (1.75 g, 43%) as a colourless oil.

Example A58

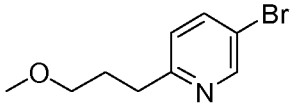
Preparation of intermediate 58: 5-Bromo-2-(2-methoxy-2-methyl-propyl)-pyridine



A 60% suspension of sodium hydride in mineral oils (2.36 g, 58.9 mmol) was added portionwise to a stirred solution of **intermediate 57** (2.36 g, 58.9 mmol) in tetrahydrofuran (10 ml). The mixture was stirred at 0 °C for 30 min. and then iodomethane (3.67 ml, 58.9 mmol) was added. The mixture was stirred at room temperature for 18 h. and then further 60% suspension of sodium hydride in mineral oils (2.36 g, 58.9 mmol) and iodomethane (3.67 ml, 58.9 mmol) were added. The mixture was stirred at room temperature for 3 h. and then the solvents were evaporated *in vacuo*. The crude product was diluted with dichloromethane and washed with a saturated solution of ammonium chloride and a saturated solution of sodium hydrogen carbonate. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; ethyl acetate in dichloromethane 0/100 to 10/90). The desired fractions were collected and concentrated *in vacuo* to yield **intermediate 58** (6.90 g, 53%).

Example A59

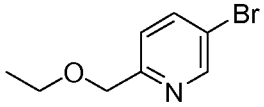
Preparation of intermediate 59: 5-Bromo-2-(3-methoxy-propyl)-pyridine



1,2-Dibromoethane (0.237 ml, 2.75 mmol) was added to a stirred suspension of zinc (3.6 g, 55.0 mmol) in dry *N,N*-dimethylformamide (40 ml). The mixture was stirred at 90 °C for 30 min. under nitrogen and then allowed to warm to room temperature. Chlorotrimethylsilane (0.09 ml, 0.69 mmol) was added and the mixture was stirred at room temperature for 15 min. A solution of **intermediate 44** (5.5 g, 27.5 mmol) in tetrahydrofuran (20ml) was added dropwise and the mixture was stirred at 45 °C for 2.5 h. The excess zinc was allowed to settle for 1 h and the supernatant liquid was transferred via *cannula* to a mixture of 2,5-dibromopyridine (2.17 g, 9.17 mmol) and bis(triphenylphosphine)palladium dichloride (0.212 g, 0.18 mmol). The mixture was stirred at 55 °C for 4 h. under nitrogen, then the solvents were evaporated *in vacuo*. The crude product was partitioned between dichloromethane and a saturated solution of sodium hydrogen carbonate. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica, ethyl acetate in dichloromethane 0/100 to 20/80). The desired fractions were collected and concentrated *in vacuo* to yield **intermediate 59** (1.4 g, 66%).

Example A60

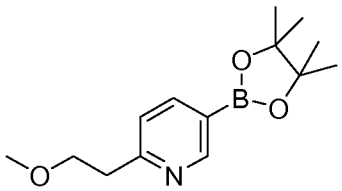
Preparation of intermediate 60: 5-Bromo-2-ethoxymethyl-pyridine



A 60% suspension of sodium hydride in mineral oils (0.073 g, 3.19 mmol) was added to a stirred solution of 5-bromo-2-(hydroxymethyl)pyridine (0.5 g, 2.66 mmol) in tetrahydrofuran (10 ml). The mixture was stirred at 0 °C for 30 min. and then iodoethane (0.498 g, 3.19 mmol) was added. The mixture was stirred at 60 °C for 18 h., then diluted with diethyl ether and washed with a saturated solution of ammonium chloride in water. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo* to yield **intermediate 60** (0.520 g, 90%) as a colourless oil.

Example A61

Preparation of intermediate 61: 2-(2-Methoxy-ethyl)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine

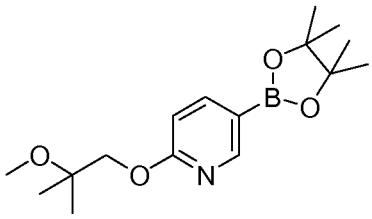


[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium (II) (0.061 g, 0.083 mmol) was added to a stirred suspension of **intermediate 56** (0.6 g, 2.77 mmol), 4,4,4′,4′,5,5,5′,5′-octamethyl-2,2′-bi-1,3,2-dioxaborolane (0.846 g, 3.33 mmol) and potassium acetate (0.817 g, 8.33 mmol) in a mixture of 1,4-dioxane (9 ml) and *N,N*-dimethylformamide (1.2 ml). The mixture was stirred at 150 °C for 40 min. in a sealed tube under nitrogen and under microwave irradiation. The mixture was filtered through a pad of diatomaceous earth, and the filtrate diluted with dichloromethane and washed with water. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo* to yield **intermediate 61** (1.1 g, 64%, 43% purity) used in next step without further purification. LCMS: 264 $[M+H]^+$; R_t: 1.55 min (method 5).

The following intermediates were prepared from the indicated precursors according to a protocol analogous to **A61**.

Example A62

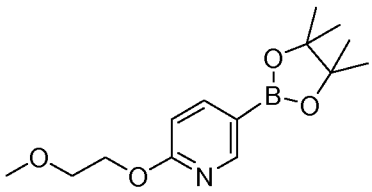
Preparation of intermediate 62: 2-(2-Methoxy-2-methyl-propoxy)- 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine



From **intermediate 46** in dimethylsulfoxide as solvent, 80 °C, 4h. Extraction with heptane yielded **intermediate 62** as a colourless oil (97%).

Example A63

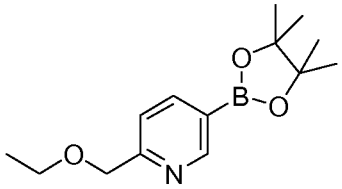
Preparation of intermediate 63: 2-(2-Methoxy-ethoxy)- 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine



From **intermediate 47** in dimethylsulfoxide as solvent, 80 °C, 4h. Extraction with heptane yielded **intermediate 63** as a colourless oil (93%).

Example A64

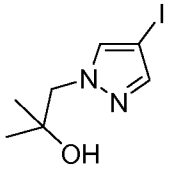
Preparation of intermediate 64: 2-Ethoxymethyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine



From **intermediate 60** in dimethylsulfoxide as solvent, 80 °C, 4h. Extraction with heptane yielded **intermeiate 64** as a colourless oil (84%).

Example A65

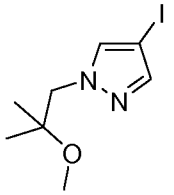
Preparation of intermediate 65: 1-(4-Iodo-pyrazol-1-yl)-2-methyl-propan-2-ol



A mixture of 4-iodopyrazole (3 g, 15.47 mmol), 1-chloro-2-methyl-2-propanol and cesium carbonate (8.06 g, 24.75 mmol) in *N*,*N*-dimethylformamide (30 ml) was stirred at 160°C for 40 min in a sealed tube, under microwave irradiation. The mixture was diluted with water and extracted with dichloromethane. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; ethyl acetate in heptane 20/80 to 40/60). The desired fractions were collected and concentrated *in vacuo* to yield **intermediate 65** (3.98 g, 97%) as a white solid.

Example A66

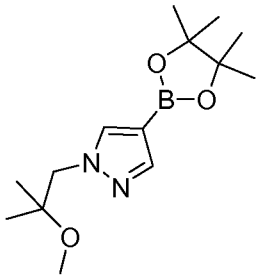
Preparation of intermediate 66: 4-Iodo-1-(2-methoxy-2-methyl-propyl)-*1H*-pyrazole



A 60% dispersion of sodium hydride in mineral oils (1.85 g, 46.23 mmol) was added portionwise to a stirred solution of **intermediate 65** (4.1 g, 15.41 mmol) in tetrahydrofuran (70 ml) at 0°C. The mixture was stirred at room temperature for 15 min and then dimethyl sulfate (3.67 ml, 66.26 mmol) was added. The mixture was stirred at room temperature for a further 18 h. and then partitioned between dichloromethane and a saturated solution of sodium hydrogen carbonate. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; ethyl acetate in heptane 0/100 to 20/80). Desired fractions were collected and concentrated *in vacuo* to yield **intermediate 66** (3.32 g, 74%) as a colorless oil.

Example A67

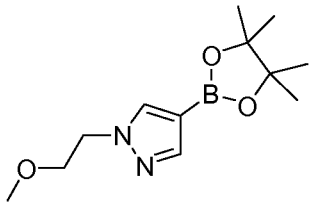
Preparation of intermediate 67: 1-(2-Methoxy-2-methyl-propyl)-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-*1H*-pyrazole



[1,1'-bis(diphenylphosphino)]dichloropalladium(II) (0.026g, 0.36 mmol) was added to a stirred solution of **intermediate 66** (1.18 g, 4.21 mmol), bis(pinacolato)diboron (1.28 g, 5.06 mmol) and potassium acetate (1.24 g, 12.64 mmol) in dimethylsulfoxide (15 ml). The mixture was stirred at 80 °C for 16 h. in a sealed tube under nitrogen. After cooling to room temperature, the mixture was partitioned between water and heptane and then filtered over cotton to remove the resulting black slurry. The organic layer was separated and the aqueous layer extracted with heptane. The combined organic layers were dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo* to yield **intermediate 67** (0.96 g, 81%) which was used in the next step without further purification.

Example A68

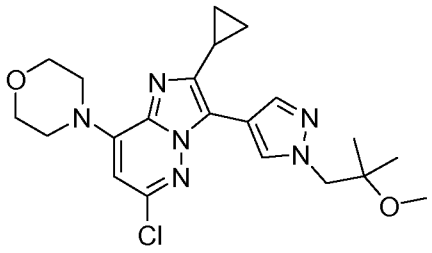
Preparation of intermediate 68: 1-(2-Methoxy-ethyl)-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-*1H*-pyrazole



A mixture of 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-*1H*-pyrazole (1 g, 5.15 mmol), 2-bromoethyl methyl ether (0.63 ml, 6.7 mmol) and cesium carbonate (2.52 g, 7.73 mmol) in *N*,*N*-dimethylformamide (7 ml) was stirred at 150 °C for 30 min. under microwave irradiation. The mixture was partitioned between water and diethyl ether. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; ethyl acetate in heptane 30/70). The desired fractions were collected and concentrated *in vacuo* to yield **intermediate 68** (0.88 g, 68%) as a pale yellow oil.

Example A69

Preparation of intermediate 69: 6-chloro-2-cyclopropyl-3-[1-(2-methoxy-2-methylpropyl)-*1H*-pyrazol-4-yl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine

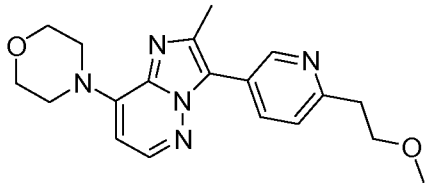


Tetrakis(triphenylphosphine)palladium(0) (0.068 g, 0.059 mmol) was added to a stirred solution of **intermediate 34** (0.30 g, 0.84 mmol) and **intermediate 67** (0.446 g, 1.59 mmol) in a mixture of 1,4-dioxane (20 ml) and a saturated solution of sodium carbonate (6 ml). The mixture was stirred at 150 °C for 15 min, in a sealed tube under nitrogen and under microwave irradiation. The mixture was diluted with dichlorometane and washed with water. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica: 7 M solution of ammonia in methanol in dichloromethane 0/100 to 2/98). The desired fractions were collected and concentrated and the crude product purified again by flash column chromatography (silica; ethyl acetate in heptane 10/90 to 50/50). The desired fractions were collected and concentrated *in vacuo* to yield **intermediate 69** (0.216 g, 59%). LCMS: 431 $[M+H]^+$; R_t: 4.30 min (method 1). This compound is also a final compound (compound 150).

B. Preparation of the final compounds

Example B1

Preparation of compound 1: 3-[6-(2-methoxyethyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine



Palladium (II) acetate (0.066 g, 0.294 mmol) was added to a stirred solution of **intermediate 14** (1.5 g, 5.89 mmol), **intermediate A56** (1.91 g, 8.83 mmol), butyldi-1-adamantylphosphine (0.211 g, 0.59 mmol) and potassium phosphate (3.75 g, 17.7 mmol) in *N*,*N*-dimethylformamide (10 ml). The mixture was stirred at room temperature for 15 min. and then at 120 °C for 24 h. in a sealed tube under nitrogen. The mixture was diluted with diethyl ether and washed with a 1% potassium hydroxide solution. The organic layer was separated, dried ($MgSO_4$), filtered and the solvents

evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; 7 M solution of ammonia in methanol in dichloromethane 0/100 to 40/60). The desired fractions were collected and concentrated *in vacuo*. The crude product was triturated from diisopropyl ether to yield **compound 1** (1.74 g, 84%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.54 (s, 3 H), 3.13 (t, J=6.7 Hz, 2 H), 3.39 (s, 3 H), 3.83 (t, J=6.8 Hz, 2 H), 3.88 - 4.04 (m, 8 H), 6.10 (d, J=5.5 Hz, 1 H), 7.36 (d, J=8.1 Hz, 1 H), 7.98 (dd, J=8.1, 2.1 Hz, 1 H), 7.99 (d, J=5.5 Hz, 1 H), 8.80 (d, J=2.3 Hz, 1 H).

For compound 1, the hydrochloride salt (.HCl) (mp = 164.8 °C with decomposition); the maleate salt (.$C_4H_4O_4$) (mp = 113.8 °C) and the monohydrate (.H_2O) (DSC: dehydration at about 88 °C followed by melt at 131.9 °C), were obtained following the procedures described below.

For the formation of the hydrochloride salt (compound 1a):
To a stirred solution of compound 1 (0.5 g, 1.41 mmol) in 2-butanone (7.50 mL) was added hydrogen chloride (1 N, 1.27 mL, 1.27 mmol). The mixture was concentrated *in vacuo* till dry at 50 °C, then 2-butanone (7.50 mL) was added. Formation of a white solid was observed and the suspension was further stirred at room temperature overnight. The solid was filtered off and dried overnight at 50 °C to yield the hydrochloride salt (0.397 g, 72%) as a white solid.

For the formation of the maleate salt (compound 1b):
To a mixture of compound 1 (1.00 g, 2.83 mmol) and (*Z*)-2-butenedioic acid (344.85 mg, 2.97 mmol), was added 1-methoxy-2-propanol (15.00 mL) and the mixture was heated to 40 °C then cooled down to 0 °C and stirred overnight at 0 °C. Precipitation was observed, with formation of very fine solids, giving the reaction mixture an almost milky appearance. A small amount of these solids was set aside and used subsequently as seeding material (see below). The mixture was heated to 50 °C. The solvent was partially evaporated to a volume of 10 mL and the reaction mixture was seeded with original solids at 45 °C. Stirring was continued at 45 °C for 4 hours, then at 40 °C for 2 hours and continued at 20 °C overnight. The resulting solid was filtered off, washed once with a very small amount of propylene glycol monomethyl ether (PGME) and once with methyl tert-butyl ether (MTBE) and dried overnight at 45 °C, to yield the maleate salt (850 mg, 64%) as a white to slightly yellow solid.

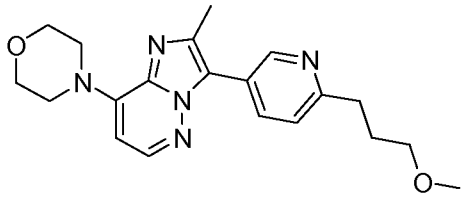
For the formation of the hydrate (compound 1c), two different procedures were used:

a) water (2 mL) was added to the solid compound (20 mg) and allowed to slurry at 70 °C for 30 minutes. The heat was turned off and the solution mixture was allowed to continue to slurry at room temperature for 3 days.
b) water (4 mL) was added to the solid compound (200 mg) and allowed to slurry at room temperature for 5 days.
The product was then filtered off and dried to yield the hydrate as a solid.

The following compounds were prepared from the indicated precursors according to a protocol analogous to **B1**.

Example B2

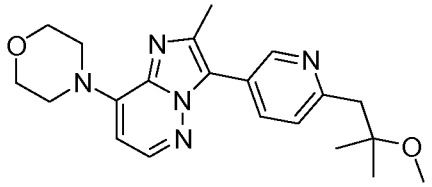
Preparation of compound 2: 3-[6-(3-methoxypropyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine



From **intermediate 14** and **intermediate 59**. Flash column chromatography (silica; ethyl acetate in heptane 20/80 to 40/60) and precipitation from methanol yielded **compound 2** as a white solid (55%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.99 - 2.17 (m, 2 H), 2.54 (s, 3 H), 2.93 (t, J=7.5 Hz, 2 H), 3.37 (s, 3 H), 3.48 (t, J=6.4 Hz, 2 H), 3.90 - 4.01 (m, 8 H), 6.10 (d, J=5.8 Hz, 1 H), 7.31 (d, J=7.8 Hz, 1 H), 7.97 (dd, J=8.1, 2.3 Hz, 1 H), 7.99 (d, J=5.8 Hz, 1 H), 8.78 (d, J=1.7 Hz, 1 H).

Example B3

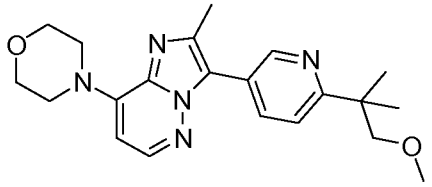
Preparation of compound 3: 3-[6-(2-methoxy-2-methylpropyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine



From **intermediate 14** and **intermediate 58**. Flash column chromatography (silica; methanol in dichloromethane 0/100 to 2/98) yielded **compound 3** as a white solid (56%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.16 (s, 6 H), 2.44 (s, 3 H), 2.96 (s, 2 H), 3.22 (s, 3 H), 3.80 (br t, *J*=4.9 Hz, 4 H), 3.97 (dd, *J*=4.9, 4.4 Hz, 4 H), 6.37 (d, *J*=5.8 Hz, 1 H), 7.40 (d, *J*=8.1 Hz, 1 H), 7.99 (dd, *J*=8.1, 2.3 Hz, 1 H), 8.10 (d, *J*=5.5 Hz, 1 H), 8.74 (d, *J*=2.1 Hz, 1 H).

Example B4

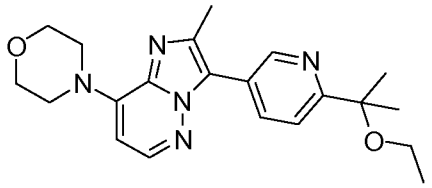
Preparation of compound 4: 3-[6-(2-methoxy-1,1-dimethylethyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine



From **intermediate 14** and **intermediate 54**. Flash column chromatography (silica; ethyl acetate in dichloromethane 0/100 to 100/0) yielded **compound 4** as a white solid (74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.41 (s, 6 H), 2.55 (s, 3 H), 3.34 (s, 3 H), 3.62 (s, 2 H), 3.85 - 4.05 (m, 8 H), 6.10 (d, *J*=5.5 Hz, 1 H), 7.49 (dd, *J*=8.3, 0.7 Hz, 1 H), 7.99 (d, *J*=5.5 Hz, 1 H), 8.01 (dd, *J*=8.3, 2.3 Hz, 1 H), 8.84 (dd, *J*=2.1, 0.7 Hz, 1 H).

Example B5

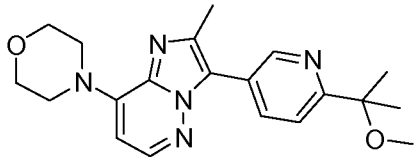
Preparation of compound 5: 3-[6-(1-ethoxy-1-methylethyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine



From **intermediate 14** and **intermediate 48**. Flash column chromatography (silica; ethyl acetate in heptane 0/100 to 100/0) and precipitation from diethyl ether yielded **compound 5** as a white solid (92%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.16 (t, *J*=7.1 Hz, 3 H), 1.53 (s, 6 H), 2.46 (s, 3 H), 3.32 (q, *J*=6.9 Hz, 2 H), 3.80 (br. t, *J*=4.9 Hz, 4 H), 3.98 (dd, *J*=4.9, 4.3 Hz, 4 H), 6.38 (d, *J*=5.8 Hz, 1 H), 7.68 (d, *J*=8.4 Hz, 1 H), 8.05 - 8.17 (m, 2 H), 8.79 (d, *J*=1.7 Hz, 1 H).

Example B6

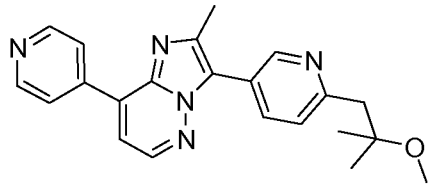
Preparation of compound 6: 3-[6-(1-methoxy-1-methylethyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine



From **intermediate 14** and **intermediate 49**. Flash column chromatography (silica; ethyl acetate in heptane 0/100 to 100/0) and precipitation from diethyl ether yielded **compound 6** as a white solid (92%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.53 (s, 6 H), 2.47 (s, 3 H), 3.13 (s, 3 H), 3.80 (br. t, *J*=4.9 Hz, 4 H), 3.98 (dd, *J*=4.9, 4.3 Hz, 4 H), 6.39 (d, *J*=5.8 Hz, 1 H), 7.67 (d, *J*=8.1 Hz, 1 H), 8.05 - 8.16 (m, 2 H), 8.81 (d, *J*=1.7 Hz, 1 H).

Example B7

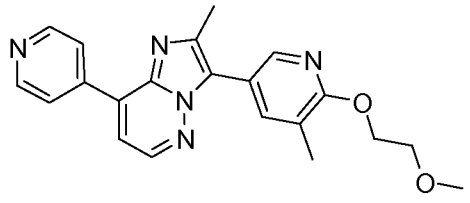
Preparation of compound 7: 3-[6-(2-methoxy-2-methylpropyl)-3-pyridinyl]-2-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine



From **intermediate 20** and **intermediate 58**. Flash column chromatography (silica; 7 M solution of ammonia in methanol in dichloromethane 0/100 to 2/98), reverse phase HPLC (0.1% solution of formic acid in acetonitrile 80/20 to 0/100) and precipitation from diethyl ether yielded **compound 7** as a white solid (54%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.18 (s, 6 H), 2.57 (s, 3 H), 2.99 (s, 2 H), 3.23 (s, 3 H), 7.46 (d, *J*=8.1 Hz, 1 H), 7.71 (d, *J*=4.9 Hz, 1 H), 8.07 (dd, *J*=8.1, 2.3 Hz, 1 H), 8.32 (d, *J*=6.2 Hz, 2 H), 8.65 (d, *J*=4.9 Hz, 1 H), 8.78 - 8.86 (m, 3 H).

Example B8

Preparation of compound 8: 3-[6-(2-methoxyethoxy)-5-methyl-3-pyridinyl]-2-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine

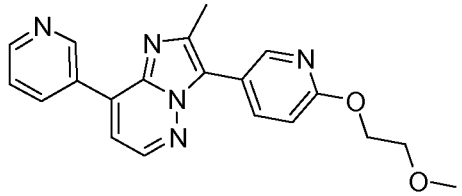


From **intermediate 20** and **intermediate 45**. Flash column chromatography (silica; 7 M solution of ammonia in methanol in dichloromethane 0/100 to 2/98) and precipitation from diethyl ether yielded **compound 8** as a yellow solid (79%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.25 (s, 3 H), 2.53 (s, 3 H), 3.35 (s, 3 H), 3.73 (br. t, *J*=4.6 Hz, 2 H), 4.50 (br. t, *J*=4.9 Hz, 2 H), 7.68 (d, *J*=4.9 Hz, 1 H), 7.88 - 7.93 (m, 1

H), 8.30 (d, *J*=1.7 Hz, 1 H), 8.32 (d, *J*=6.4 Hz, 2 H), 8.63 (d, *J*=4.9 Hz, 1 H), 8.82 (d, *J*=6.1 Hz, 2 H).

Example B9

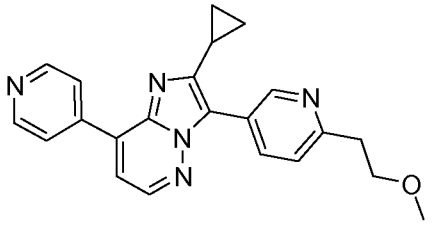
Preparation of compound 9: 3-[6-(2-methoxyethoxy)-3-pyridinyl]-2-methyl-8-(3-pyridinyl)-imidazo[1,2-b]pyridazine



From **intermediate 19** and **intermediate 47**. Flash column chromatography (silica; 7 M solution of ammonia in methanol in dichloromethane 0/100 to 2/98), reverse phase HPLC (0.1% solution of ammonium formate/ammonium hydroxide buffer pH 9 and acetonitrile 20/80 to 0/100) and precipitation from diethyl ether yielded **compound 9** as a pale yellow solid (73%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.54 (s, 3 H), 3.33 (s, 3 H), 3.71 (br. t, *J*=4.6 Hz, 2 H), 4.47 (br. t, *J*=4.6 Hz, 2 H), 7.04 (d, *J*=8.7 Hz, 1 H), 7.64 (d, *J*=4.9 Hz, 1 H), 7.65 (d, *J*=4.6 Hz, 1 H), 8.08 (dd, *J*=8.5, 2.5 Hz, 1 H), 8.49 (d, *J*=2.6 Hz, 1 H), 8.59 (d, *J*=4.6 Hz, 1 H), 8.72 (dt, *J*=8.0, 1.9 Hz, 1 H), 8.74 (dd, *J*=4.8, 1.6 Hz, 1 H), 9.47 (d, *J*=2.0 Hz, 1 H).

Example B10

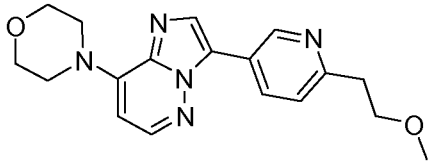
Preparation of compound 10: 2-cyclopropyl-3-[6-(2-methoxyethyl)-3-pyridinyl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine



From **intermediate 18** and **intermediate 56**. Flash column chromatography (silica; ethyl acetate in dichloromethane 30/70 to 100/0) and precipitation from diisopropyl ether yielded **compound 10** as a pale yellow solid (31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.02 - 1.09 (m, 2 H), 1.19 - 1.28 (m, 2 H), 2.14 - 2.26 (m, 1 H), 3.17 (t, *J*=6.6 Hz, 2 H), 3.41 (s, 3 H), 3.86 (t, *J*=6.7 Hz, 2 H), 7.26 (d, *J*=4.6 Hz, 1 H), 7.42 (d, *J*=8.1 Hz, 1 H), 8.14 (dd, *J*=8.1, 2.3 Hz, 1 H), 8.14 - 8.19 (m, *J*=6.0 Hz, 2 H), 8.37 (d, *J*=4.6 Hz, 1 H), 8.81 (d, *J*=6.0 Hz, 2 H), 9.03 (d, *J*=2.1 Hz, 1 H).

Example B11

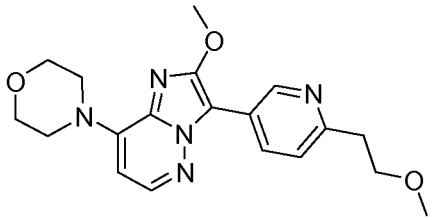
Preparation of compound 11: 3-[6-(2-methoxyethyl)-3-pyridinyl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine



From **intermediate 17** and **intermediate 56**. Flash column chromatography (silica; 7 M solution of ammonia in methanol in dichloromethane 0/100 to 3/97) and filtration through an Isolute SCX-2 cartridge followed by elution with a 7 M solution of ammonia in methanol yielded **compound 11** as a white solid (83%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 3.01 (t, *J*=6.6 Hz, 2 H), 3.25 (s, 3 H), 3.72 (t, *J*=6.5 Hz, 2 H), 3.79 (br. t, *J*=4.9 Hz, 4 H), 4.00 (dd, *J*=4.9, 4.3 Hz, 4 H), 6.42 (d, *J*=5.8 Hz, 1 H), 7.41 (d, *J*=8.4 Hz, 1 H), 8.06 (s, 1 H), 8.24 (d, *J*=5.8 Hz, 1 H), 8.38 (dd, *J*=8.1, 2.3 Hz, 1 H), 9.14 (d, *J*=1.7 Hz, 1 H).

Example B12

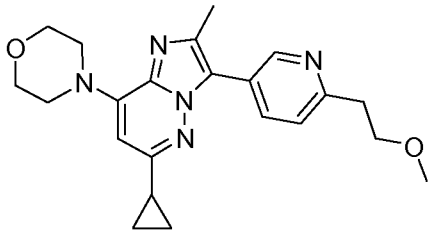
Preparation of compound 12: 2-methoxy-3-[6-(2-methoxyethyl)-3-pyridinyl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine



From **intermediate 15** and **intermediate 56**. Flash column chromatography (silica; 7 M solution of ammonia in methanol in dichloromethane 0/100 to 3/97) and precipitation from diisopropyl ether yielded **compound 12** as a white solid (83%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.98 (t, *J*=6.7 Hz, 2 H), 3.25 (s, 3 H), 3.71 (t, *J*=6.6 Hz, 2 H), 3.80 (dd, *J*=5.1, 4.4 Hz, 4 H), 3.92 (dd, *J*=5.1, 4.4 Hz, 4 H), 4.06 (s, 3 H), 6.48 (d, *J*=6.0 Hz, 1 H), 7.38 (d, *J*=8.3 Hz, 1 H), 8.21 (d, *J*=5.8 Hz, 1 H), 8.35 (dd, *J*=8.3, 2.3 Hz, 1 H), 9.15 (d, *J*=2.3 Hz, 1 H).

Example B13

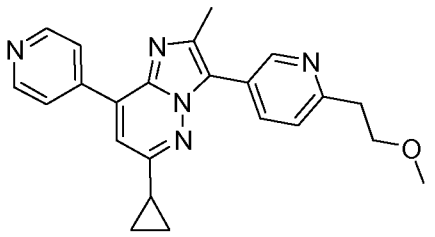
Preparation of compound 13: 6-cyclopropyl-3-[6-(2-methoxyethyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine



From **intermediate 23** and **intermediate 56**. Flash column chromatography (silica; ethyl acetate in heptane 0/100 to 100/0) yielded **compound 13** as a white solid (85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.93 - 0.96 (m, 4 H), 1.88 - 1.97 (m, 1 H), 2.53 (s, 3 H), 3.13 (t, *J*=6.7 Hz, 2 H), 3.40 (s, 3 H), 3.84 (t, *J*=6.7 Hz, 2 H), 3.87 - 3.92 (m, 4 H), 3.92 - 3.98 (m, 4 H), 5.98 (s, 1 H), 7.33 (d, *J*=8.1 Hz, 1 H), 7.97 (dd, *J*=8.1, 2.3 Hz, 1 H), 8.85 (d, *J*=1.6 Hz, 1 H).

Example B14

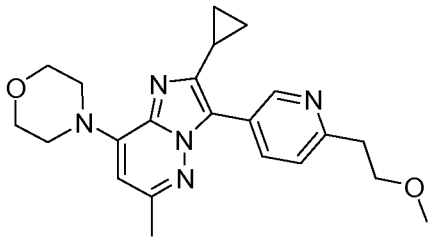
Preparation of compound 14: 6-cyclopropyl-3-[6-(2-methoxyethyl)-3-pyridinyl]-2-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine



From **intermediate 24** and **intermediate 56**. Flash column chromatography (silica; methanol and ethyl acetate in heptane 0/30/70 to 2/98/0) and precipitation from diisopropyl ether yielded **compound 14** as a pale yellow solid (85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.03 - 1.15 (m, 4 H), 2.08 - 2.18 (m, 1 H), 2.63 (s, 3 H), 3.16 (t, *J*=6.5 Hz, 2 H), 3.41 (s, 3 H), 3.87 (t, *J*=6.6 Hz, 2 H), 7.06 (s, 1 H), 7.39 (d, *J*=8.1 Hz, 1 H), 8.00 (dd, *J*=8.1, 2.3 Hz, 1 H), 8.05 (d, *J*=6.1 Hz, 2 H), 8.81 (d, *J*=6.1 Hz, 2 H), 8.91 (d, *J*=1.7 Hz, 1 H).

Example B15

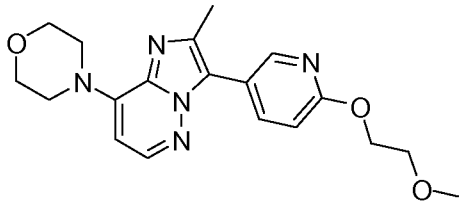
Preparation of compound 15: 2-cyclopropyl-3-[6-(2-methoxyethyl)-3-pyridinyl]-6-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine



From **intermediate 25**) and **intermediate 56**. Flash column chromatography (silica; ethyl acetate in heptane 20/80 to 50/50) yielded **compound 15** as a white solid (47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.91 - 0.98 (m, 2 H), 1.03 - 1.13 (m, 2 H), 2.05 - 2.15 (m, 1 H), 2.41 (s, 3 H), 3.13 (t, *J*=6.8 Hz, 2 H), 3.40 (s, 3 H), 3.84 (t, *J*=6.7 Hz, 2 H), 3.90 (br. s., 8 H), 5.96 (s, 1 H), 7.35 (d, *J*=8.1 Hz, 1 H), 8.13 (dd, *J*=8.1, 2.3 Hz, 1 H), 9.02 (d, *J*=2.3 Hz, 1 H).

Example B16

Preparation of compound 16: 3-[6-(2-methoxyethoxy)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine

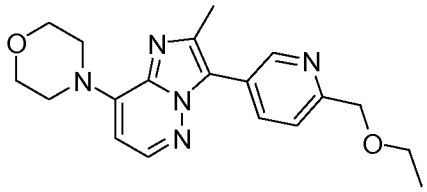


Tetrakis(triphenylphosphine)palladium (0) (0.034 g, 0.009 mmol) was added to a stirred solution of **intermediate 26** (0.2 g, 0.58 mmol) and **intermediate 63** (0.243 g, 0.87 mmol), in a mixture of 1,4-dioxane (5 ml) and a saturated solution of sodium carbonate (3 ml). The mixture was stirred at 80 °C for 16 h. in a sealed tube under nitrogen and then diluted with dichloromethane and washed with water. The organic layer was separated, filtered over cotton, and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; ethyl acetate in dichloromethane 0/100 to 50/50). The desired fractions were collected and concentrated *in vacuo* to yield **compound 16** (0.151 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.51 (s, 3 H), 3.46 (s, 3 H), 3.78 (t, *J*=4.6 Hz, 2 H), 3.86 - 4.06 (m, 8 H), 4.55 (dd, *J*=4.9, 4.4 Hz, 2 H), 6.08 (d, *J*=5.5 Hz, 1 H), 6.96 (d, *J*=8.8 Hz, 1 H), 7.92 (dd, *J*=8.6, 2.3 Hz, 1 H), 7.97 (d, *J*=5.5 Hz, 1 H), 8.37 (d, *J*=2.3 Hz, 1 H).

The following compounds were prepared from the indicated precursors according to a protocol analogous to **B16**.

Example B17

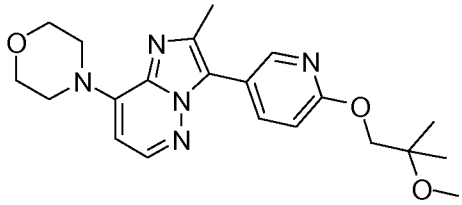
Preparation of compound 17: 3-[6-(ethoxymethyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine



From **intermediate 26** and **intermediate 64**. Conditions: 150°C, 15 min, microwave irradiation. Flash column chromatography (silica; 7 M solution of ammonia in methanol in dichloromethane 0/100 to 2/98) yielded **compound 17** as a white solid (75%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.21 (t, *J*=7.1 Hz, 3 H), 2.45 (s, 3 H), 3.60 (q, *J*=7.0 Hz, 2 H), 3.79 (dd, *J*=5.1, 4.4 Hz, 4 H), 3.98 (br. t, *J*=4.6 Hz, 4 H), 4.60 (s, 2 H), 6.37 (d, *J*=5.8 Hz, 1 H), 7.56 (d, *J*=8.1 Hz, 1 H), 8.10 (dd, *J*=8.1, 2.1 Hz, 1 H), 8.10 (d, *J*=5.8 Hz, 1 H), 8.78 (d, *J*=2.1 Hz, 1 H).

Example B18

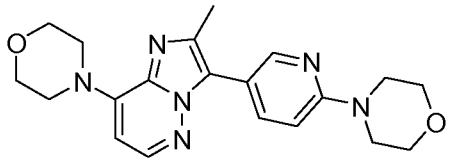
Preparation of compound 18: 3-[6-(2-methoxy-2-methylpropoxy)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine



From **intermediate 26** and **intermediate 62**. Conditions: 140°C, 20 min, microwave irradiation. Flash column chromatography (silica; ethyl acetate in dichloromethane 0/100 to 50/50) yielded **compound 18** as a white solid (82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.32 (s, 6 H), 2.51 (s, 3 H), 3.32 (s, 3 H), 3.90 - 4.01 (m, 8 H), 4.30 (s, 2 H), 6.08 (d, 1 H), 6.98 (dd, *J*=8.6, 0.5 Hz, 1 H), 7.93 (dd, *J*=8.6, 2.3 Hz, 1 H), 7.97 (d, *J*=5.5 Hz, 1 H), 8.37 (d, *J*=1.8 Hz, 1 H).

Example B19

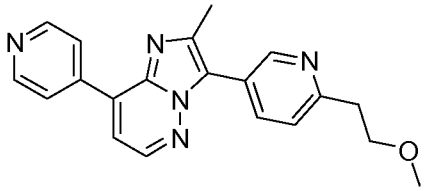
Preparation of compound 19: 2-methyl-8-(4-morpholinyl)-3-[6-(4-morpholinyl)-3-pyridinyl]-imidazo[1,2-b]pyridazine



From **intermediate 26** and commercially available 1-[5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridin-2-yl]morpholine. Flash column chromatography (silica; ethyl acetate in heptanes 0/100 to 40/60) and flash column chromatography (silica; ethyl acetate and dichloromethane in heptane from 0/0/100 to 20/80/0) yielded **compound 19** as a white solid (69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.51 (s, 3 H), 3.58 (dd, *J*=5.1, 4.6 Hz, 4 H), 3.85 (dd, *J*=5.1, 4.6 Hz, 4 H), 3.95 (br. s., 8 H), 6.06 (d, *J*=5.8 Hz, 1 H), 6.78 (d, *J*=8.8 Hz, 1 H), 7.86 (dd, *J*=8.8, 2.3 Hz, 1 H), 7.97 (d, *J*=5.5 Hz, 1 H), 8.43 (d, *J*=2.3 Hz, 1 H).

Example B20

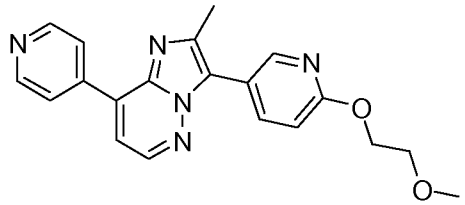
Preparation of compound 20: 3-[6-(2-methoxyethyl)-3-pyridinyl]-2-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine



From **intermediate 33** and **intermediate 61**. Conditions: 150 °C, 5 min, microwave irradiation. Flash column chromatography (silica; 7 M solution of ammonia in methanol in dichloromethane 0/100 to 4/96) and precipitation from diisopropyl ether yielded **compound 20** as a white solid (45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.66 (s, 3 H), 3.16 (t, *J*=6.6 Hz, 2 H), 3.41 (s, 3 H), 3.86 (t, *J*=6.7 Hz, 2 H), 7.24 (d, *J*=4.9 Hz, 1 H), 7.41 (d, *J*=8.1 Hz, 1 H), 8.02 (dd, *J*=8.1, 2.3 Hz, 1 H), 8.09 (d, *J*=6.2 Hz, 2 H), 8.40 (d, *J*=4.9 Hz, 1 H), 8.83 (d, *J*=6.2 Hz, 2 H), 8.88 (d, *J*=2.3 Hz, 1 H).

Example B21

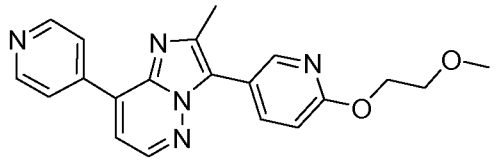
Preparation of compound 21: 3-[6-(2-methoxyethoxy)-3-pyridinyl]-2-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine



From **intermediate 33** and **intermediate 63**. Conditions: 150 °C, 15 min, microwave irradiation. Flash column chromatography (silica; ethyl acetate in heptane 0/100 to 100/0) and precipitation from diethyl ether yielded **compound 21** as a white solid (44%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.55 (s, 3 H), 3.34 (s, 3 H), 3.72 (br t, *J*=4.6 Hz, 2 H), 4.48 (br t, *J*=4.6 Hz, 2 H), 7.05 (d, *J*=8.7 Hz, 1 H), 7.70 (d, *J*=4.6 Hz, 1 H), 8.09 (dd, *J*=8.7, 2.3 Hz, 1 H), 8.33 (dd, *J*=4.6, 1.7 Hz, 2 H), 8.49 (d, *J*=2.0 Hz, 1 H), 8.63 (d, *J*=4.6 Hz, 1 H), 8.82 (dd, *J*=4.6, 1.7 Hz, 2 H).

Example B21a

Preparation of compound 21a: 3-[6-(2-methoxyethoxy)-3-pyridinyl]-2-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine hydrochloride salt

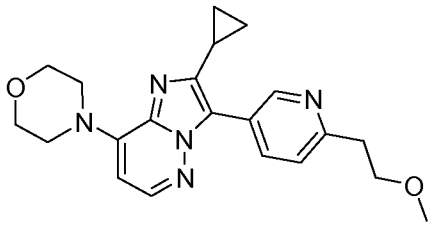


. 1.7HCl

Hydrochloric acid (38.16 mL, 2M solution in diethyl ether) was added to a solution of **compound 21** (19.7 g, 54.51 mmol) in a mixture of diethylether (220 mL) and dichloromethane (600 mL). The mixture was stirred at room temperature for 2.5 h and then concentrated *in vacuo*. Diethyl ether was then added, and the solid was filtered, washed with diethyl ether and dried overnight *in vacuo*, to yield **compound 21a** (20.94 g, 91%) as an orange solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.57 (s, 3 H), 3.33 (s, 3 H), 3.67 - 3.76 (m, 2 H), 4.42 - 4.51 (m, 2 H), 7.07 (d, *J*=8.7 Hz, 1 H), 7.94 (d, *J*=4.6 Hz, 1 H), 8.09 (dd, *J*=8.5, 2.5 Hz, 1 H), 8.50 (d, *J*=2.3 Hz, 1 H), 8.77 (d, *J*=4.9 Hz, 1 H), 8.88 - 8.98 (m, 2 H), 9.09 - 9.17 (m, 2 H).

Example B22

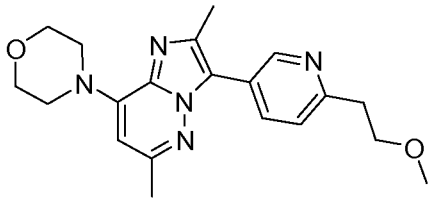
Preparation of compound 22: 2-cyclopropyl-3-[6-(2-methoxyethyl)-3-pyridinyl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine



From **intermediate 27** and **intermediate 61**. Conditions: 150 °C, 15 min, microwave irradiation. Flash column chromatography (silica; 7 M solution of ammonia in methanol in dichloromethane 0/100 to 7/93) and reverse phase HPLC (0.1% solution of ammonium formate/ammonium hydroxide buffer pH 9 and acetonitrile 80/20 to 0/100) yielded **compound 22** as a white solid (14%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.92 - 1.01 (m, 2 H), 1.06 - 1.13 (m, 2 H), 2.05 - 2.16 (m, 1 H), 3.13 (t, *J*=6.7 Hz, 2 H), 3.39 (s, 3 H), 3.83 (t, *J*=6.7 Hz, 2 H), 3.88 - 4.05 (m, 8 H), 6.06 (d, *J*=5.8 Hz, 1 H), 7.37 (d, *J*=8.1 Hz, 1 H), 7.96 (d, *J*=5.8 Hz, 1 H), 8.10 (dd, *J*=8.0, 2.2 Hz, 1 H), 8.96 (d, *J*=2.3 Hz, 1 H).

Example B23

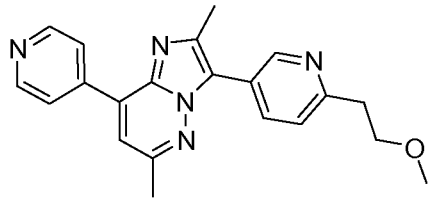
Preparation of compound 23: 3-[6-(2-methoxyethyl)-3-pyridinyl]-2,6-dimethyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine



From **intermediate 28** and **intermediate 61**. Conditions: 150 °C, 15 min, microwave irradiation. Flash column chromatography (silica; 7 M solution of ammonia in methanol in dichloromethane 0/100 to 2/98) and reverse phase HPLC (0.1% solution of ammonium formate/ammonium hydroxide buffer pH 9 and acetonitrile 80/20 to 0/100) yielded **compound 23** as a white solid (14%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.41 (s, 3 H), 2.52 (s, 3 H), 3.13 (t, *J*=6.7 Hz, 2 H), 3.40 (s, 3 H), 3.84 (t, *J*=6.7 Hz, 2 H), 3.88 - 3.97 (m, 8 H), 5.99 (s, 1 H), 7.34 (d, *J*=8.1 Hz, 1 H), 7.99 (dd, *J*=8.1, 2.3 Hz, 1 H), 8.86 (d, *J*=2.3 Hz, 1 H).

Example B24

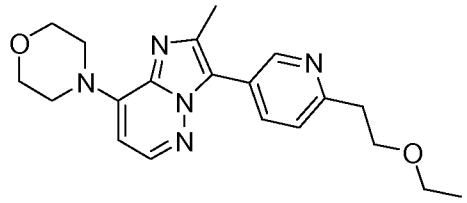
Preparation of compound 24: 3-[6-(2-methoxyethyl)-3-pyridinyl]-2,6-dimethyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine



From **intermediate 30** and **intermediate 61**. Conditions: 150 °C, 15 min, microwave irradiation. Flash column chromatography (silica; 7 M solution of ammonia in methanol in dichloromethane 0/100 to 2/98) and flash column chromatography (silica; 7 M solution of ammonia in methanol in dichloromethane 0/100 to 5/95) and precipitation from diisopropyl ether yielded **compound 24** as a yellow solid (29%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.62 (s, 3 H), 2.64 (s, 3 H), 3.16 (t, *J*=6.5 Hz, 2 H), 3.41 (s, 3 H), 3.87 (t, *J*=6.6 Hz, 2 H), 7.12 (s, 1 H), 7.40 (d, *J*=8.1 Hz, 1 H), 8.02 (dd, *J*=8.1, 2.3 Hz, 1 H), 8.06 (d, *J*=6.1 Hz, 2 H), 8.81 (d, *J*=6.1 Hz, 2 H), 8.93 (d, *J*=1.7 Hz, 1 H).

Example B25

Preparation of compound 25: 3-[6-(2-ethoxyethyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine

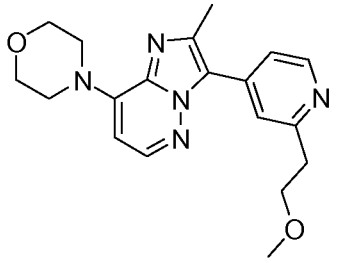


A 60% dispersion of sodium hydride in mineral oils (0.2 g, 5 mmol) was added portionwise to a stirred solution of **intermediate 38** (0.2 g, 0.62 mmol) in ethanol (8 ml). The mixture was stirred at 100 °C for 16h. in a sealed tube and then poured onto water and extracted with dichloromethane. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; 7 M solution of ammonia in methanol in dichloromethane 0/100 to 1/99). The desired fractions were collected and concentrated *in vacuo* to yield **compound 25** (0.042 g, 18%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.10 (t, *J*=6.9 Hz, 3 H), 2.44 (s, 3 H), 3.02 (t, *J*=6.8 Hz, 2 H), 3.46 (q, *J*=6.9 Hz, 2 H), 3.72 - 3.84 (m, 6 H), 3.97 (dd, *J*=4.9, 4.3 Hz, 4 H), 6.37 (d, *J*=5.8 Hz, 1 H), 7.44 (d, *J*=8.1 Hz, 1 H), 7.99 (dd, *J*=8.1, 2.3 Hz, 1 H), 8.09 (d, *J*=5.8 Hz, 1 H), 8.74 (d, *J*=1.7 Hz, 1 H).

The following compound was prepared from the indicated precursors according to aprotocol analogous to **B25**.

Example B26

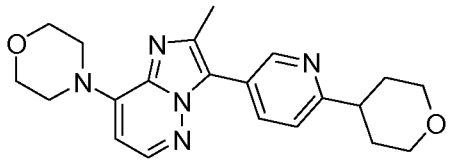
Preparation of compound 26: 3-[2-(2-methoxyethyl)-4-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine



From **intermediate 40** and sodium methoxide. Flash column chromatography (silica; ethyl acetate in heptane 20/80 to 100/0) yielded **compound 26** as a white solid (69%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.58 (s, 3 H), 3.15 (t, *J*=6.8 Hz, 2 H), 3.38 (s, 3 H), 3.83 (t, *J*=6.8 Hz, 2 H), 3.88 - 4.03 (m, 8 H), 6.13 (d, *J*=5.5 Hz, 1 H), 7.54 (dd, *J*=5.2, 1.7 Hz, 1 H), 7.60 (br. s., 1 H), 8.03 (d, *J*=5.8 Hz, 1 H), 8.64 (d, *J*=5.2 Hz, 1 H).

Example B27

Preparation of compound 27: 2-methyl-8-(4-morpholinyl)-3-[6-(tetrahydro-*2H*-pyran-4-yl)-3-pyridinyl]-imidazo[1,2-b]pyridazine

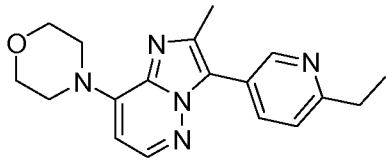


10% Palladium on charcoal (0.069 g) was added to a suspension of **intermediate 41** (0.245 g, 0.65 mmol) and ammonium formate (0.122 g, 1.95 mmol) in methanol (10 ml). The mixture was stirred at 85 °C for 4 h. and then more 10% palladium on charcoal (0.69 g) and ammonium formate (0.122 g, 1.95 mmol) were added. The mixture was stirred at 90 °C for a further 16h. and then filtered through a pad of diatomaceous earth and the filtrate concentrated *in vacuo*. The crude product was diluted with dichloromethane and washed with water. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; ethyl acetate in heptane 30/70 to 100/0). The desired fractions were collected and evaporated to yield **compound 27** (0.21 g, 86%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.83 - 2.06 (m, 4 H), 2.54 (s, 3 H), 2.94 - 3.10 (m, 1 H), 3.51 - 3.65 (m, 2 H), 3.87 - 4.03 (m, 8 H), 4.07 -

4.19 (m, 2 H), 6.10 (d, *J*=5.8 Hz, 1 H), 7.32 (d, *J*=8.1 Hz, 1 H), 7.99 (d, *J*=5.5 Hz, 1 H), 8.02 (dd, *J*=8.2, 2.2 Hz, 1 H), 8.80 (d, *J*=2.1 Hz, 1 H).

Example B28

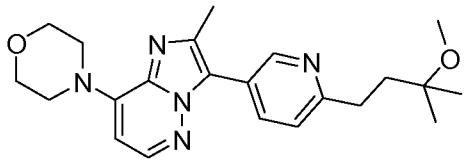
Preparation of compound 28: 3-(6-ethyl-3-pyridinyl)-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine



10% Palladium on charcoal (0.405 g) was added to a suspension of **intermediate 38** (2.45 g, 7.62 mmol) in a mixture of methanol (90 ml) and ethyl acetate (90 ml). The mixture was hydrogenated (atmospheric pressure) at room temperature for 16 h. and then filtered through a pad of diatomaceous earth. The filtrate was concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica; ethyl acetate in dichloromethane 0/100 to 100/0). The desired fractions were collected and concentrated *in vacuo*. The crude product was precipitated from diethyl ether to yield **compound 28** (0.675 g, 27%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.28 (t, *J*=7.7 Hz, 3 H), 2.44 (s, 3 H), 2.82 (q, *J*=7.6 Hz, 2 H), 3.79 (br t, *J*=4.9 Hz, 4 H), 3.97 (dd, *J*=4.9, 4.3 Hz, 4 H), 6.36 (d, *J*=5.8 Hz, 1 H), 7.41 (d, *J*=8.1 Hz, 1 H), 7.99 (dd, *J*=8.1, 2.3 Hz, 1 H), 8.09 (d, *J*=5.8 Hz, 1 H), 8.73 (d, *J*=1.7 Hz, 1 H).

Example B29

Preparation of compound 29: 3-[6-(3-methoxy-3-methylbutyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine

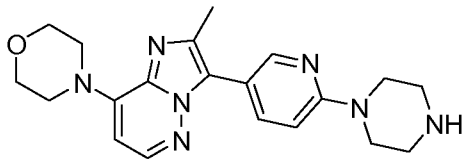


1,2-Dibromoethane (0.016 ml, 0.19 mmol) was added to a stirred suspension of zinc (0.337 g, 5.17 mmol) in dry *N,N*-dimethylformamide (8 ml). The mixture was stirred at 90 °C for 30 min. under nitrogen and then allowed to cool down to room temperature. Chlorotrimethylsilane (0.006 ml, 0.048 mmol) was added and the mixture was stirred at room temperature for 15 min. A solution of **intermediate 43** (0.7 g, 2.58 mmol) in tetrahydrofuran (3 ml) was added dropwise and the mixture was stirred at 50 °C for 1.5 h. The excess zinc was allowed to settle for 1 h and the supernatant liquid was transferred via *cannula* to a second flask charged with **intermediate 35** (0.21 g, 0.64 mmol) and tetrakis(triphenylphosphine)palladium (0) (0.015 g, 0.013 mmol). The

mixture was stirred at 55 °C for 16 h. under nitrogen, and then a saturated solution of ammonium chloride was added. The mixture was extracted with ethyl acetate and the organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; methanol in dichloromethane 0/100 to 2/98). The desired fractions were collected and concentrated to yield **compound 29** (0.071 g, 28%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.26 (s, 6 H), 1.86 - 2.07 (m, 2 H), 2.53 (s, 3 H), 2.79 - 2.99 (m, 2 H), 3.26 (s, 3 H), 3.80 - 4.11 (m, 8 H), 6.09 (d, *J*=5.5 Hz, 1 H), 7.32 (d, *J*=8.1 Hz, 1 H), 7.96 (dd, *J*=8.1, 1.6 Hz, 1 H), 7.98 (d, *J*=5.5 Hz, 1 H), 8.78 (br. s., 1 H).

Example B30

Preparation of compound 30: 2-methyl-8-(4-morpholinyl)-3-[6-(1-piperazinyl)-3-pyridinyl]-imidazo[1,2-b]pyridazine

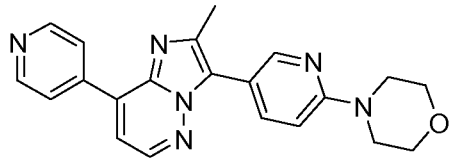


Piperazine (4.68 g, 54.4 mmol) was added to a stirred solution of **intermediate 35** (2.7 g, 6.80 mmol) in acetonitrile (24 ml). The mixture was stirred at 120 °C for 1 d. in a sealed tube and then diluted with dichloromethane and washed with water. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by column chromatography (silica; 7 M solution of ammonia in methanol in dichloromethane 0/100 to 3/97). The desired fractions were collected and concentrated *in vacuo* and the crude product was precipitated from diisopropyl ether to yield **compound 30** (1.64 g, 39%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.75 (s, 1 H), 2.51 (s, 3 H), 3.01 (br. t, *J*=5.1 Hz, 4 H), 3.59 (dd, *J*=5.3, 4.9 Hz, 4 H), 3.83 - 4.07 (m, 8 H), 6.06 (d, *J*=5.8 Hz, 1 H), 6.78 (d, *J*=9.0 Hz, 1 H), 7.83 (dd, J=8.9, 2.4 Hz, 1 H), 7.97 (d, J=5.5 Hz, 1 H), 8.41 (d, J=2.3 Hz, 1 H).

The following compound was prepared from the indicated precursors according to a protocol analogous to that used of **B30**.

Example B31

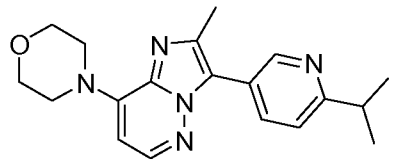
Preparation of compound 31: 2-methyl-3-[6-(4-morpholinyl)-3-pyridinyl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine



From **intermediate 37** and morpholine. Flash column chromatography (silica; 7 M solution of ammonia in methanol in dichloromethane 0/100 to 2/98) and precipitation from diethyl ether yielded **compound 31** as an orange solid (80%). M. p. > 300 ° C (decomposition). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.53 (s, 3 H), 3.55 (dd, *J*=5.2, 4.6 Hz, 4 H), 3.74 (br. t, *J*=4.6 Hz, 4 H), 7.02 (d, *J*=8.7 Hz, 1 H), 7.64 (d, *J*=4.9 Hz, 1 H), 7.91 (dd, *J*=8.8, 2.5 Hz, 1 H), 8.32 (d, *J*=6.1 Hz, 2 H), 8.45 (d, *J*=2.0 Hz, 1 H), 8.59 (d, *J*=4.9 Hz, 1 H), 8.81 (d, *J*=6.4 Hz, 2 H).

Example B32

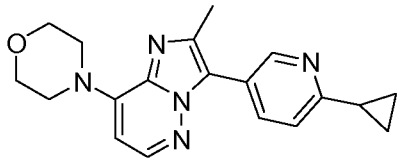
Preparation of compound 32: 2-methyl-3-[6-(1-methylethyl)-3-pyridinyl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine



A 2M solution of isopropylmagnesium chloride in tetrahydrofuran (0.758, 1.52) was added to a stirred solution of **intermediate 35** (0.25 g, 0.76 mmol) and [1,3-bis(diphenylphosphino)propane]dichloronickel (II) (0.021 g, 0.038 mmol) in tetrahydrofuran (5 ml) at 0°C. The mixture was allowed to warm to room temperature over 1 h. and then stirred for a further 2h. A 10% solution of ammonium chloride solution was added and the mixture was extracted with dichloromethane. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; 7 M solution of ammonia in methanol in dichloromethane 0/100 to 2/98). The less pure fractions were evaporated *in vacuo* and the residue purified again by flash column chromatography (silica, ethyl acetate in heptane 20/80 to 60/40). The desired fractions were combined and concentrated *in vacuo* to yield **compound 32** (0.116 g, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.36 (d, *J*=6.9 Hz, 6 H), 2.54 (s, 3 H), 3.13 (spt, *J*=6.9 Hz, 1 H), 3.85 - 4.07 (m, 8 H), 6.09 (d, *J*=5.5 Hz, 1 H), 7.32 (d, *J*=8.1 Hz, 1 H), 7.98 (dd, *J*=8.1, 2.1 Hz, 1 H), 7.99 (d, *J*=5.5 Hz, 1 H), 8.79 (d, *J*=2.1 Hz, 1 H).

Example B33

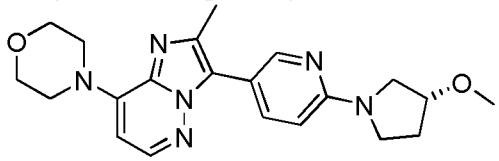
Preparation of compound 33: 3-(6-cyclopropyl-3-pyridinyl)-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine



Palladium (II) acetate (0.031 g, 0.14 mmol) was added to a stirred solution of **intermediate 35** (0.3 g, 0.91 mmol), cyclopropylboronic acid (0.117 g, 1.37 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (0.244 g, 0.594 mmol) and potassium phosphate (0.11 g, 0.27 mmol) in toluene (5 ml). The mixture was stirred at 80 °C for 1 d. in a sealed tube under nitrogen and then diluted with dichloromethane and washed with water. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; ethyl acetate in heptane 20/80 to 100/0). The desired fractions were collected and concentrated *in vacuo* and the crude product triturated with diisopropyl ether to yield **compound 33** (0.091 g, 30%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.00 - 1.06 (m, 2 H), 1.06 - 1.12 (m, 2 H), 2.06 - 2.13 (m, 1 H), 2.51 (s, 3 H), 3.90 - 4.00 (m, 8 H), 6.08 (d, *J*=5.8 Hz, 1 H), 7.26 (d, *J*=7.5 Hz, 4 H), 7.89 (dd, *J*=8.1, 2.0 Hz, 1 H), 7.97 (d, *J*=5.5 Hz, 1 H), 8.69 (d, *J*=2.3 Hz, 1 H).

Example B34

Preparation of compound 34: 3-[6-[(3*R*)-3-methoxy-1-pyrrolidinyl]-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine

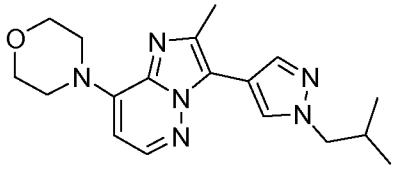


A mixture of **intermediate 35** (0.2 g, 0.61 mmol), (R)-(+)-3-pyrrolidinol (0.21 g, 2.43 mmol) and diisopropylethylamine (0.158 ml, 0.91 mmol) was stirred at 120 °C for 3 h. The mixture was diluted with dichloromethane and extracted with a saturated solution of ammonium chloride. The organic layer was separated, dried ($MgSO_4$), filtered and the solvents evaporated *in vacuo*. The crude product was dissolved in tetrahydrofuran (10 ml) and sodium *tert*-butoxide (0.34 g, 3.03 mmol), 18-crown-6 (0.024 g, 0.091 mmol) and iodomethane (0.378 ml, 6.06 mmol) were added. The mixture was stirred at room temperature for 18 h., then diluted with dichloromethane and washed with water. The organic layer was separated, dried ($MgSO_4$), filtered and the solvents evaporated *in vacuo*. The crude product was purified by column chromatography (silica;

dichloromethane). The desired fractions were collected and concentrated *in vacuo* to yield **compound 34** (0.091 g, 30%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.08 - 2.24 (m, 2 H), 2.50 (s, 3 H), 3.38 (s, 3 H), 3.59 (dd, *J*=8.5, 5.9 Hz, 2 H), 3.64 - 3.71 (m, 2 H), 3.90 - 3.98 (m, 8 H), 4.08 - 4.14 (m, 1 H), 6.04 (d, *J*=5.5 Hz, 1 H), 6.51 (d, *J*=8.7 Hz, 1 H), 7.78 (dd, *J*=8.7, 2.3 Hz, 1 H), 7.95 (d, *J*=5.5 Hz, 1 H), 8.37 (d, *J*=2.3 Hz, 1 H).

Example B35

Preparation of compound 35: 2-methyl-3-[1-(2-methylpropyl)-*1H*-pyrazol-4-yl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine

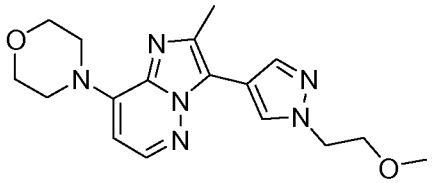


Tetrakis(triphenylphosphine)palladium(0) (0.017 g, 0.015 mmol) was added to a stirred solution of **intermediate 26** (0.2 g, 0.58 mmol) and 1-isobutyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*1H*-pyrazole (0.18 g, 0.73 mmol) in a mixture of 1,4-dioxane (8 ml) and a saturated solution of sodium carbonate (2 ml). The mixture was stirred at 140 °C for 20 min. in a sealed tube under nitrogen, under microwave irradiation. The mixture was filtered through a pad of diatomaceous earth and the filtrate diluted with dichlorometane and extracted with water. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; ethyl acetate in dichloromethane 0/100 to 40/60). The desired fractions were collected and concentrated *in vacuo* to yield **compound 35** (0.14 mg, 71 %) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.97 (d, J=6.6 Hz, 6 H), 2.30 (spt, J=6.7 Hz, 1 H), 2.61 (s, 3 H), 3.89 - 3.97 (m, 8 H), 4.01 (d, J=7.2 Hz, 2 H), 6.06 (d, J=5.8 Hz, 1 H), 8.01 (s, 1 H), 8.05 (d, J=5.5 Hz, 1 H), 8.17 (s, 1 H).

The following compounds were prepared from the indicated precursors according to a protocol analogous to that of **B35**.

Example B36

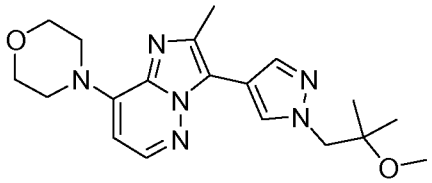
Preparation of compound 36: 3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine



From **intermediate 32** and **intermediate 68**). Flash column chromatography (silica; 7 M solution of ammonia in methanol in dichloromethane 0/100 to 4/96) and precipitation from diisopropyl ether yielded **compound 36** as a white solid (57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.61 (s, 3 H), 3.36 (s, 3 H), 3.82 (t, J=5.4 Hz, 2 H), 3.94 (br. s, 8 H), 4.39 (t, J=5.4 Hz, 2 H), 6.06 (d, J=5.8 Hz, 1 H), 8.04 (s, 1 H), 8.05 (d, J=5.5 Hz, 1 H), 8.24 (s, 1 H).

Example B37

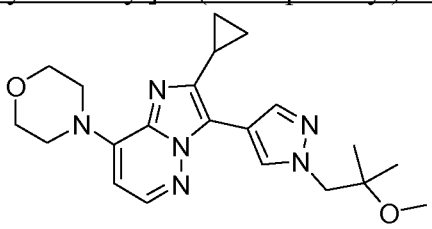
Preparation of compound 37: 3-[1-(2-methoxy-2-methylpropyl)-*1H*-pyrazol-4-yl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine



From **intermediate 26** and **intermediate 67**. Flash column chromatography (silica; ethyl acetate and dichloromethane in heptane 0/100/0 to 0/0/100 to 80/0/20), filtration through Isolute SCX-2 cartridge and precipitation from diethyl ether yielded **compound 37** as a white solid (29%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.12 (s, 6 H), 2.50 (s, 3 H), 3.20 (s, 3 H), 3.78 (br t, *J*=4.9 Hz, 4 H), 3.96 (br t, *J*=4.9 Hz, 4 H), 4.23 (s, 2 H), 6.31 (d, *J*=5.8 Hz, 1 H), 8.00 (s, 1 H), 8.16 (d, *J*=5.8 Hz, 1 H), 8.26 (s, 1 H).

Example B38

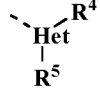
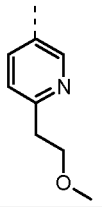
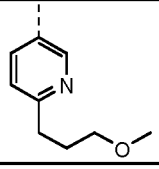
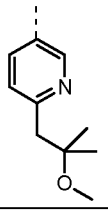
Preparation of compound 38: 2-cyclopropyl-3-[1-(2-methoxy-2-methylpropyl)-*1H*-pyrazol-4-yl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine

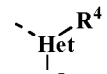
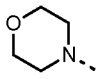
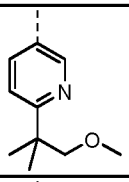
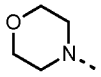
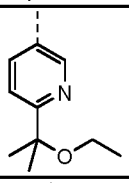
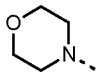
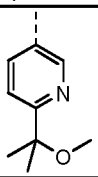
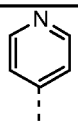
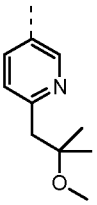
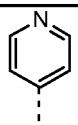
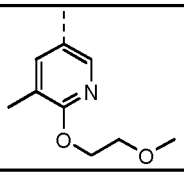
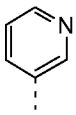
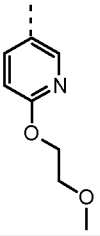
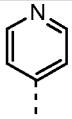
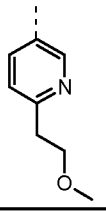
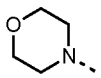
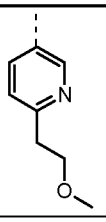


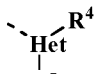
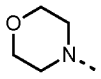
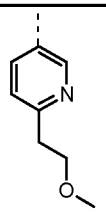
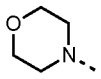
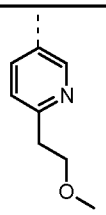
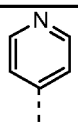
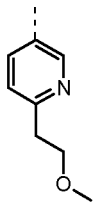
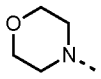
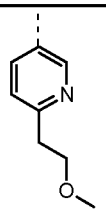
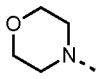
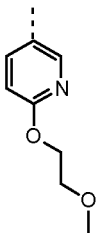
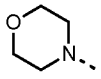
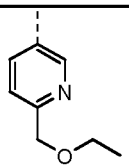
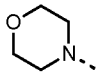
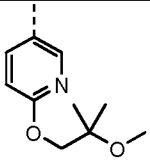
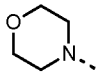
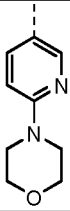
10% Palladium on activated charcoal (0.284 g) was added to a mixture of **intermediate 69** (0.125 g, 0.29 mmol) and triethylamine (0.08 ml, 0.58 mmol) in a mixture of methanol (6 ml) and tetrahydrofuran (6 ml). The mixture was hydrogenated (atmospheric pressure) at room temperature for 24 h. and then filtered through a pad of diatomaceous earth and the filtrate was concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica; ethyl acetate in heptane 30/70 to 100/0). The desired fractions were collected and concentrated *in vacuo* to yield **compound 38** (0.116 g, 99%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.85 - 0.95 (m, 2 H), 0.95 - 1.02 (m, 2 H), 1.12 (s, 6 H), 2.15 - 2.23 (m, 1 H), 3.20 (s, 3 H), 3.71 - 3.83 (m, 4 H), 3.85 - 3.98 (m, 4 H), 4.23 (s, 2 H), 6.30 (d, *J*=5.8 Hz, 1 H), 8.09 (s, 1 H), 8.15 (d, *J*=5.5 Hz, 1 H), 8.32 (s, 1 H).

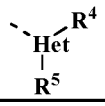
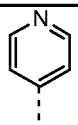
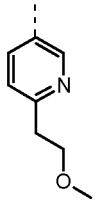
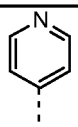
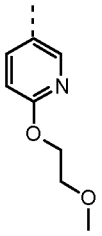
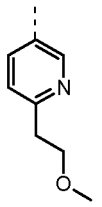
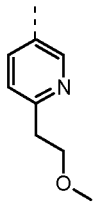
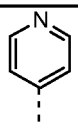
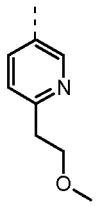
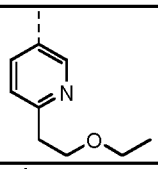
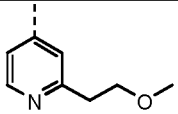
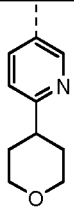
Additional compounds were prepared from the corresponding intermediates according to procedures similar to those described for the synthesis of the corresponding Examples previously described. The corresponding intermediates were prepared by procedures similar to those previously described either in the Experimental Part or in the Synthesis section. Compound **45** was isolated as the corresponding hydrochloric acid salt (.HCl). The assignment of configuration in compounds 34, 113 and 131 derives from the reagent used in the synthesis of the compounds.

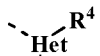
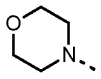
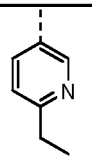
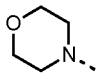
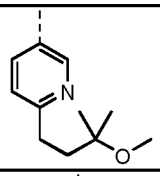
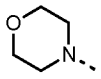
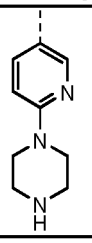
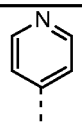
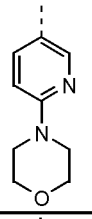
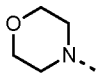
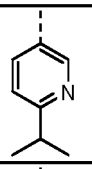
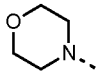
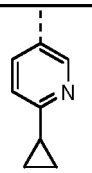
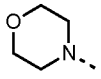
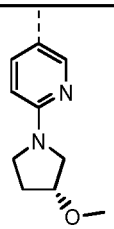
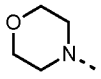
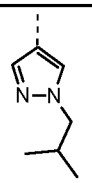
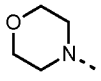
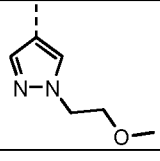
Table 1. Compounds and melting points thereof according to formula (I) prepared according to the above methods. (Dec means decomposition)

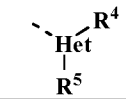
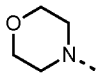
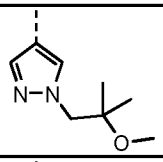
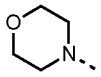
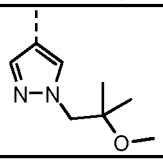
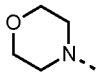
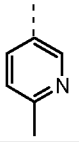
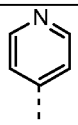
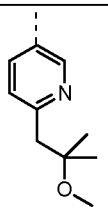
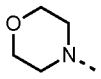
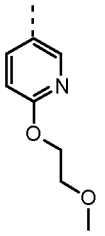
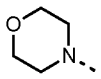
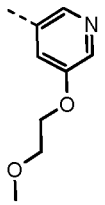
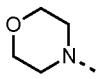
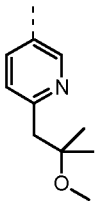
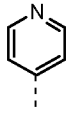
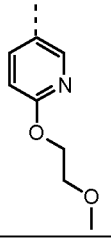
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3	B3		---CH_3	---H		101.8

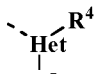
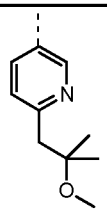
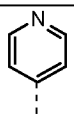
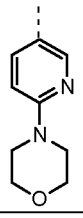
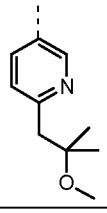
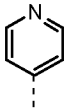
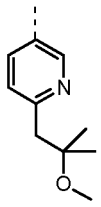
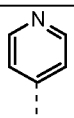
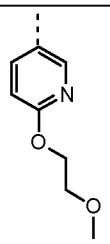
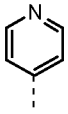
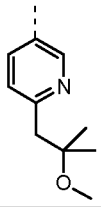
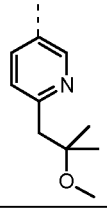
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6	B6		---CH_3	---H		132.5
7	B7		---CH_3	---H		126.1
8	B8		---CH_3	---H		159
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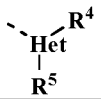
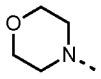
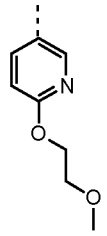
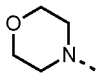
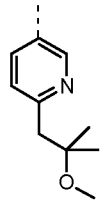
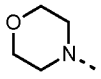
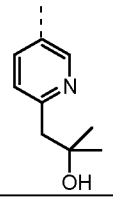
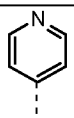
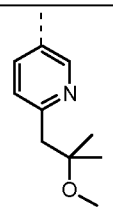
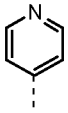
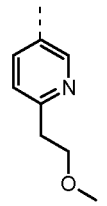
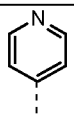
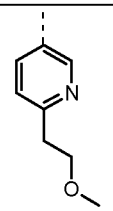
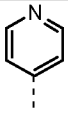
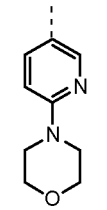
Co. No.	Ex. No.	R^1	R^2	R^3		M. p. (°C)
12	B12		---OCH_3	---H		190.7
13	B13		---CH_3			137.2
14	B14		---CH_3			> 300 Dec.
15	B15			---CH_3		122.5
16	B16		---CH_3	---H		n.d.
17	B17		---CH_3	---H		>300 Dec.
18	B18		---CH_3	---H		> 300 Dec.
19	B19		---CH_3	---H		n.d.

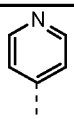
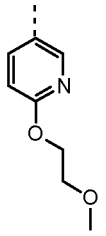
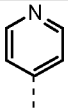
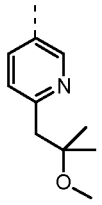
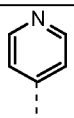
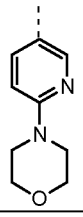
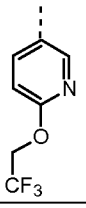
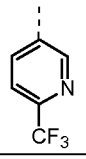
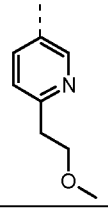
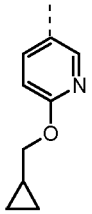
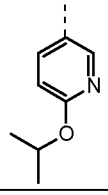
Co. No.	Ex. No.	R^1	R^2	R^3		M. p. (°C)
20	B20		---CH_3	---H		149.7
21	B21		---CH_3	---H		168.7
22	B22			---H		111.4
23	B23		---CH_3	---CH_3		115.4
24	B24		---CH_3	---CH_3		> 300 Dec.
25	B25		---CH_3	---H		n.d.
26	B26		---CH_3	---H		n.d.
27	B27		---CH_3	---H		274.4

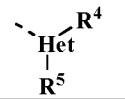
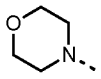
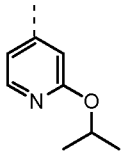
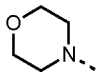
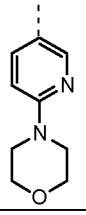
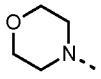
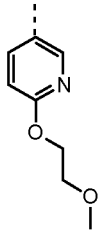
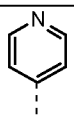
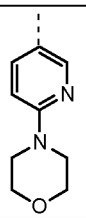
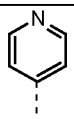
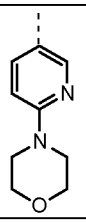
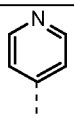
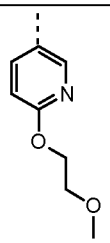
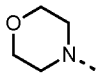
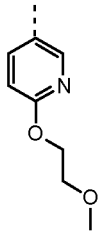
Co. No.	Ex. No.	R^1	R^2	R^3		M. p. (°C)
28	B28		---CH_3	---H		130.2
29	B29		---CH_3	---H		> 300 Dec.
30	B30		---CH_3	---H		n.d.
31	B31		---CH_3	---H		>300 Dec.
32	B35		---CH_3	---H		129.3
33	B33		---CH_3	---H		142.5
34	B34		---CH_3	---H		162
35	B35		---CH_3	---H		n.d.
36	B36		---CH_3	---H		113.7

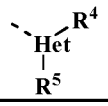
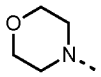
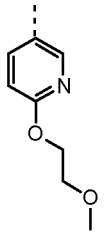
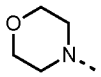
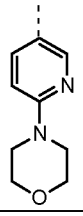
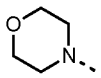
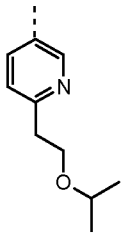
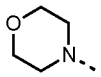
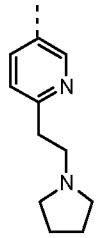
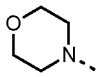
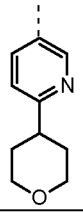
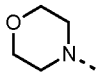
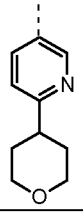
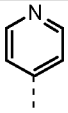
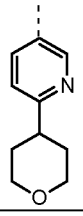
Co. No.	Ex. No.	R^1	R^2	R^3		M. p. (°C)
37	B37		---CH_3	---H		126.1
38	B38			---H		n.d.
39	B1		---CH_3	---H		176.9
40	B1		---CH_3			133.9
41	B1		---CH_3			106.2
42	B1		---CH_3			108.8
43	B1		---CH_3			128.5
44	B1			---H		146.0

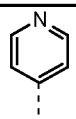
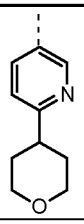
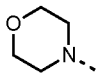
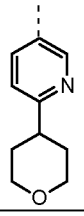
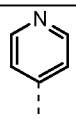
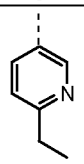
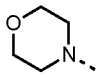
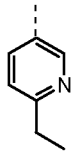
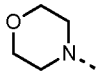
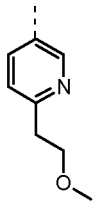
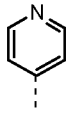
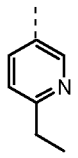
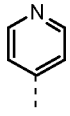
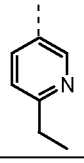
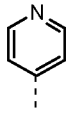
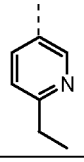
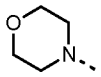
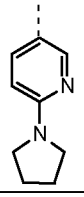
Co. No.	Ex. No.	R^1	R^2	R^3		M. p. (°C)
45	B1			---H		n.d.
46	B1			---H		> 300 Dec.
47	B1		---CH_3	---CH_3		123.5
48	B1		---CH_3	---CH_3		159.0
49	B1		---CH_3	---CH_3		128.3
50	B1			---H		114.1
51	B1		---H	---H		143.3

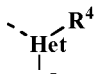
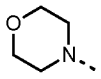
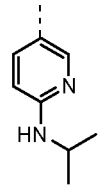
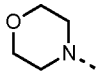
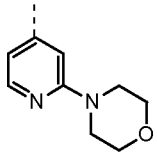
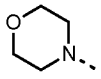
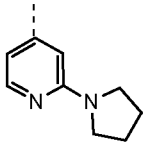
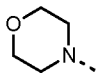
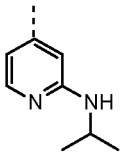
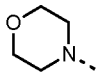
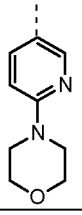
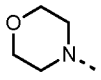
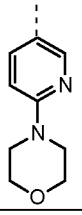
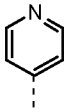
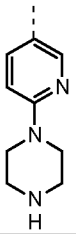
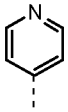
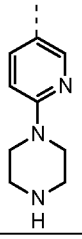
Co. No.	Ex. No.	R^1	R^2	R^3		M. p. (°C)
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53	B1			---CH_3		200.9
54	B1			---H		n.d.
55	B1			---CH_3		> 300 Dec.
56	B1			---CH_3		> 300 Dec.
57	B1		---H	---H		142.1
58	B1		---CH_3			198.1

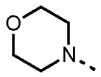
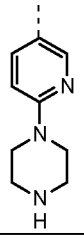
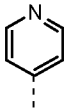
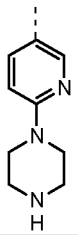
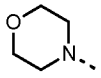
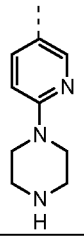
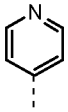
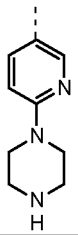
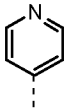
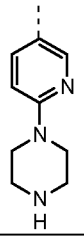
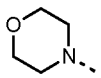
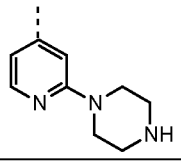
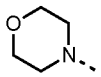
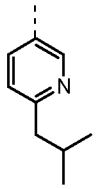
Co. No.	Ex. No.	R^1	R^2	R^3		M. p. (°C)
59	B1		---CH_3			119.3
60	B1		---H	---H		152.1
61	B1		---H	---H		167.7
62	B16		---CH_3	---H		> 300 Dec.
63	B16		---CH_3	---H		n.d.
64	B16		---CH_3	---CF_3		132.2
65	B16		---CH_3	---H		n.d.
66	B16		---CH_3	---H		n.d.

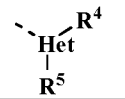
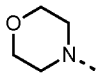
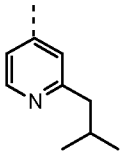
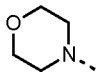
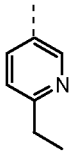
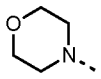
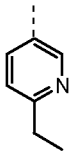
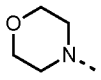
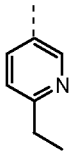
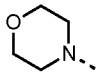
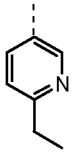
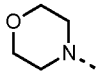
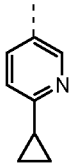
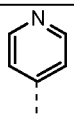
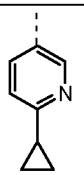
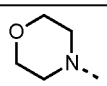
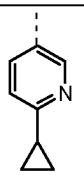
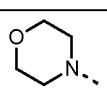
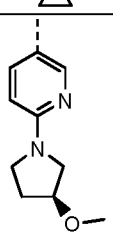
Co. No.	Ex. No.	R^1	R^2	R^3		M. p. (°C)
67	B16		---CH_3	---H		n.d.
68	B16		---CH_3	---CH_3		200.5
69	B16		---CH_3	---CH_3		239.4
70	B16		---CH_3	---CH_3		n.d.
71	B16			---CH_3		> 300 Dec.
72	B16			---CH_3		123.1
73	B16			---H		n.d.

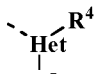
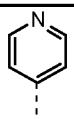
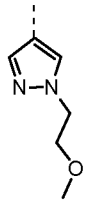
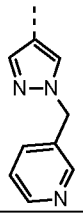
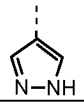
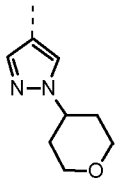
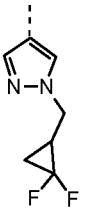
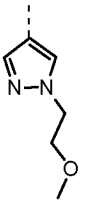
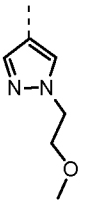
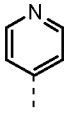
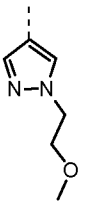
Co. No.	Ex. No.	R^1	R^2	R^3		M. p. (°C)
74	B16			---CH_3		99.7
75	B16			---CH_3		183.2
76	B25		---CH_3	---H		n.d.
77	B25		---CH_3	---H		> 300 Dec.
78	B28		---CH_3			177.4
79	B28			---CH_3		196.2
80	B28			---CH_3		195.4

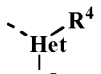
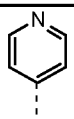
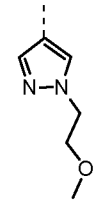
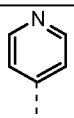
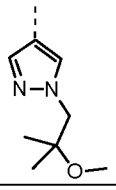
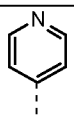
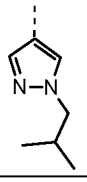
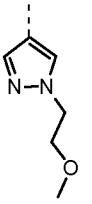
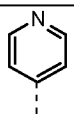
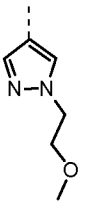
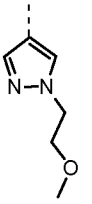
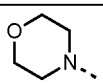
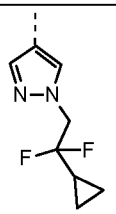
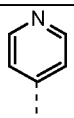
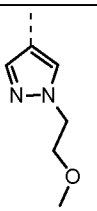
Co. No.	Ex. No.	R^1	R^2	R^3	R^4 Het R^5	M. p. (°C)
81	B28		---CH_3			n.d.
82	B28		---H	---H		n.d.
83	B29		---CH_3	---H		153.7
84	B29			---CH_3		147.2
85	B30			---CF_3		n.d.
86	B30		---CH_3			> 300 Dec.
87	B30			---H		140.3
88	B30		---CH_3	---CH_3		> 300 Dec.
89	B31		---CH_3	---H		174.3

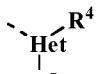
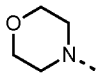
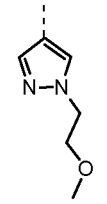
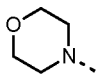
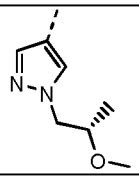
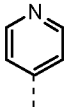
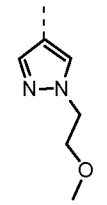
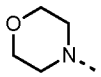
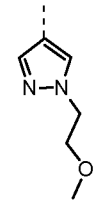
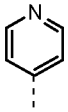
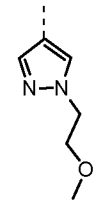
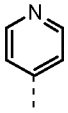
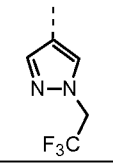
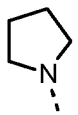
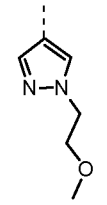
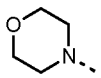
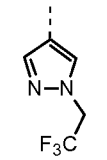
Co. No.	Ex. No.	R^1	R^2	R^3		M. p. (°C)
90	B31		---CH_3	---H		> 300 Dec.
91	B31		---CH_3	---H		200.8
92	B31		---CH_3	---H		n.d.
93	B31		---CH_3	---H		201.2
94	B31		---CH_3			191.3
95	B31			---H		n.d.
96	B31		---CH_3	---CH_3		220.2
97	B31		---CH_3	---H		> 300 Dec.

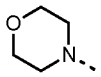
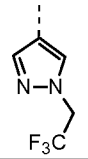
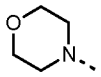
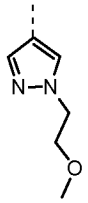
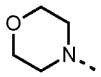
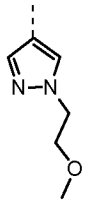
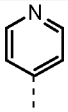
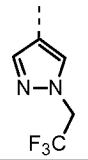
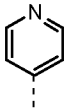
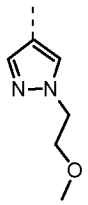
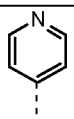
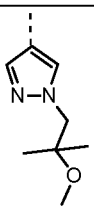
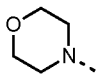
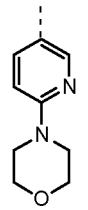
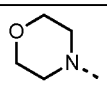
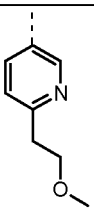
Co. No.	Ex. No.	R^1	R^2	R^3		M. p. (°C)
98	B31			---H		n.d.
99	B31		---CH_3			> 300 Dec.
100	B31			---CH_3		200.1
101	B31			---CH_3		223.2
102	B31			---H		212.1
103	B31		---CH_3	---H		n.d.
104	B33		---CH_3	---H		116.1

Co. No.	Ex. No.	R^1	R^2	R^3		M. p. (°C)
105	B33		---CH_3	---H		127.0
106	B33			---H		118.0
107	B33		---CH_3			137.4
108	B33		---CH_3	---CH_3		164.4
109	B33		---H	---H		n.d.
110	B34		---CH_3	---CH_3		154.6
111	B34		---CH_3	---H		179.6
112	B34		---H	---H		n.d.
113	B35		---CH_3	---H		n.d.

Co. No.	Ex. No.	R^1	R^2	R^3		M. p. (°C)
114	B36		---CH_3	---H		n.d.
115	B36		---CH_3	---H		n.d.
116	B36		---CH_3	---H		n.d.
117	B36		---CH_3	---H		n.d.
118	B36		---CH_3	---H		n.d.
119	B36			---H		n.d.
120	B36			---H		150.1
121	B36			---H		129.8

Co. No.	Ex. No.	R^1	R^2	R^3		M. p. (°C)
122	B36		---CF_3	---H		n.d.
123	B36		---CH_3	---H		n.d.
124	B36		---CH_3	---H		132.6
125	B36		---CH_3			138.0
126	B36		---CH_3			130.6
127	B36		---CH_2CH_3	---H		120.8
128	B36		---CH_3	---H		n.d.
129	B36		---CH_3	---CF_3		165.2

Co. No.	Ex. No.	R^1	R^2	R^3		M. p. (°C)
130	B36		---CH_3	---CF_3		173.7
131	B36		---CH_3	---H		n.d.
132	B36		---CH_2CH_3	---H		174.4
133	B36		---CH_3	---CH_3		140.3
134	B36		---CH_3	---CH_3		138.5
135	B36		---CH_3	---H		n.d.
136	B39		---CH_3	---H		n.d.
137	B39		---CH_3	---H		n.d.

Co. No.	Ex. No.	R^1	R^2	R^3		M. p. (°C)
138	B39			---H		178.0
139	B39		---CF_3	---H		132.6
140	B39		---OCH_3	---H		> 300 Dec.
141	B39			---H		n.d.
142	B39			---H		114.0
143	B39			---H		138.0
144	B39		---H	---H		190.7
145	B39		---CF_3	---H		n.d.

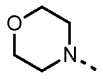
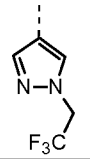
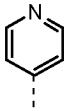
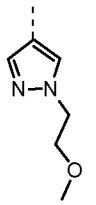
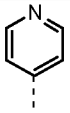
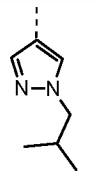
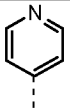
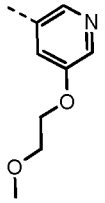
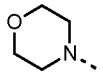
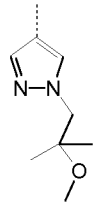
Co. No.	Ex. No.	R^1	R^2	R^3		M. p. (°C)
146	A69		---CH_3	---Cl		n.d.
147	A69		---CH_3	---Cl		> 300 Dec.
148	B36			---H		191.2
149	B1		---CH_3	---H		167.7
150	A69			---Cl		n.d.

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

LCMS data: $[M+H]^+$ means the protonated mass of the free base of the compound, R_t means retention time (in minutes), method refers to the method used for LCMS.

Co. No.	M.Wt.	$[M+H]^+$	R_t	Method
4	381	382	3.08	5
5	381	382	3.07	5
6	367	368	2.64	5
7	373	374	2.31	5

Co. No.	M.Wt.	$[M+H]^+$	R_t	Method
8	376	375	2.68	5
9	361	362	2.20	5
10	371	372	2.61	5
11	339	340	1.98	5

Co. No.	M.Wt.	$[M+H]^+$	R_t	Method
12	369	370	2.65	5
13	393	394	2.87	5
14	385	386	2.63	5
15	393	394	3.14	5
16	369	370	2.40	5
17	353	354	2.32	5
18	397	398	2.99	5
19	380	381	2.29	5
20	345	346	1.86	5
21	361	362	2.21	5
21a	361	362	2.20	5
22	379	380	2.83	5
23	367	368	3.30	1
24	359	360	2.17	5
25	367	368	2.41	5
26	353	354	2.0	5
27	379	380	2.28	5
28	323	324	2.44	5
29	395	396	2.78	5
30	379	380	1.25	5
31	372	373	2.15	5
32	337	338	3.43	2
33	335	336	1.99	5
34	394	395	3.00	5
35	340	341	3.39	1

Co. No.	M.Wt.	$[M+H]^+$	R_t	Method
36	342	343	3.02	1
37	370	371	2.31	5
38	396	397	3.03	5
39	309	310	1.98	5
40	413	414	3.06	5
41	409	410	3.26	5
42	409	410	2.72	5
43	421	422	3.31	5
44	387	388	3.03	5
45	407	408	3.33	5
46	398	399	2.92	5
47	395	396	2.81	5
48	387	388	2.61	5
49	375	376	2.55	5
50	399	400	3.08	5
51	367	368	2.44	5
52	355	356	2.32	5
53	421	422	3.61	5
54	393	394	2.74	5
55	413	414	3.36	5
56	385	386	2.89	5
57	331	332	1.76	5
58	412	413	2.92	5
59	401	402	3.03	5
60	359	360	2.19	5

Co. No.	M.Wt.	$[M+H]^+$	R_t	Method
61	358	359	3.31	1
62	393	394	4.07	1
63	380	381	2.29	5
64	421	422	3.16	5
65	365	366	3.38	5
66	353	354	3.35	5
67	353	354	3.35	5
68	394	395	2.58	5
69	383	384	2.71	5
70	386	387	2.45	5
71	412	413	3.21	5
72	401	402	2.40	5
73	395	396	3.26	5
74	409	410	3.55	5
75	420	421	3.41	5
76	381	382	2.74	5
77	392	393	1.34	5
78	419	420	3.08	5
79	419	420	3.36	5
80	411	412	3.11	5
81	411	412	2.78	5
82	365	366	2.18	5
83	315	316	2.23	5
84	363	364	3.61	5
85	447	448	3.88	5

Co. No.	M.Wt.	$[M+H]^+$	R_t	Method
86	355	356	3.07	5
87	341	342	3.03	5
88	329	330	2.56	5
89	364	365	2.84	5
90	352	353	2.56	5
91	380	381	2.28	5
92	364	365	2.72	5
93	352	353	2.51	5
94	420	421	3.16	5
95	405	406	4.34	1
96	385	386	1.26	5
97	371	372	1.08	5
98	405	406	1.86	5
99	411	412	1.68	5
100	419	420	2.07	5
101	411	412	1.89	5
102	397	398	1.68	5
103	379	380	1.33	5
104	351	352	3.20	5
105	351	352	3.07	5
106	349	350	3.28	5
107	363	364	3.33	5
108	337	338	2.78	5
109	309	310	2.35	5
110	349	350	3.10	5

Co. No.	M.Wt.	$[M+H]^+$	R_t	Method
111	327	328	2.54	5
112	321	322	2.61	5
113	394	395	2.42	5
114	334	335	2.03	4
115	375	376	2.57	1
116	284	285	1.98	1
117	368	369	2.68	1
118	374	375	3.12	2
119	368	369	2.48	5
120	370	371	2.70	5
121	362	363	2.45	5
122	388	389	2.31	5
123	362	363	2.87	2
124	332	333	2.56	5
125	382	383	2.58	5
126	374	375	2.39	5
127	356	357	2.18	5
128	388	389	2.75	5
129	402	403	2.59	5
130	410	411	2.94	5

Co. No.	M.Wt.	$[M+H]^+$	R_t	Method
131	356	357	2.81	1
132	348	349	2.69	2
133	356	357	2.75	2
134	348	349	2.64	2
135	358	359	2.84	2
136	326	327	2.91	4
137	366	367	2.69	4
138	392	393	3.11	5
139	396	397	2.63	5
140	358	359	2.30	5
141	384	385	3.08	1
142	360	361	2.95	2
143	388	389	2.84	5
144	366	367	2.16	5
145	407	408	2.88	5
146	400	401	2.7	4
147	368	369	2.67	4
148	358	359	4.11	5
149	361	362	2.11	5

D. Pharmacological examples

The compounds provided in the present invention are inhibitors of PDE10, particularly, of PDE10A. The behaviour of the PDE10 inhibitors according to Formula (I) *in vitro* and using an apomorphine induced stereotypy model *in vivo* is shown in Table 3. The *in vitro* selectivity towards PDE10A, occupancy, and results using PCP-induced hyperlocomotion, conditioned avoidance response models, SCH-23390-

induced hypolocomotion in mice and object recognition test in rats of selected compounds are shown in tables 4 to 7.

In vitro assay PDE10A

Rat recombinant PDE10A (rPDE10A2) was expressed in Sf9 cells using a recombinant rPDE10A baculovirus construct. Cells were harvested after 48 h of infection and the rPDE10A protein was purified by metal chelate chromatography on Ni-sepharose 6FF . Tested compounds were dissolved and diluted in 100% DMSO to a concentration 100 fold of the final concentration in the assay. Compound dilutions (0.4 µl) were added in 384 well plates to 20 µl of incubation buffer (50 mM Tris pH 7.8, 8.3 mM $MgCl_2$, 1.7 mM EGTA). 10µl of rPDE10A enzyme in incubation buffer was added and the reaction was started by addition of 10 µl substrate to a final concentration of 60 nM cAMP and 0.008 µCi ^{3}H-cAMP. The reaction was incubated for 60 minutes at room temperature. After incubation, the reaction was stopped with 20 µl of of stop solution consisting of 17.8 mg/ml PDE SPA (scintillation proximity assay) beads. After sedimentation of the beads during 30 minutes the radioactivity was measured in a Perkin Elmer Topcount scintillation counter and results were expressed as cpm. For blanc values the enzyme was omitted from the reaction and replaced by incubation buffer. Control values were obtained by addition of a final concentration of 1% DMSO instead of compound. The same assay principle is applied for the measurement of the affinity of the compound for other members of the PDE family with appropriate modifications in incubation buffer, substrate concentration, incubation time and stop solution. An overview of the different protocols is presented in table A. A best fit curve is fitted by a minimum sum of squares method to the plot of % of control value substracted with blanc value versus compound concentration and the half maximal inhibitory concentration (IC_{50}) value is derived from this curve.

Table A: Assay conditions for the Measurement of Phosphodiesterase activity by SPA

Enzyme	Incubation Buffer	Final Concentration Substrate	^{3}H Substrate µCi/well	Stop Solution	Incubation Time (min)
hPDE1B1	B*	1 µM cAMP	0.016	1*	30
hPDE2A	A*	10 µM cGMP	0.01	2*	40
hPDE3A	A*	0.1 µM cAMP	0.024	2*	60
hPDE4D3	A*	1 µM cAMP	0.008	1*	60
hPDE5A3	A*	1 µM cGMP	0.01	2*	60
hPDE6AB	A*	0.1 µM cGMP	0.01	2*	120

Enzyme	Incubation Buffer	Final Concentration Substrate	^{3}H Substrate µCi/well	Stop Solution	Incubation Time (min)
hPDE7A1	A*	60 nM cAMP	0.008	1*	60
hPDE8A1	A*	0.3 µM cAMP	0.01	1*	60
hPDE9A	C*	60 nM cGMP	0.008	2*	60
rPDE10A2	A*	60 nM cAMP	0.008	1*	60
hPDE11A4	A*	0.3 µM cGMP	0.01	1*	30

A* 50 mM Tris pH7.8, 1.7 mM EGTA, 8.3 mM $MgCl_2$

B* 50 mM Tris pH7.8, 8.3 mM $MgCl_2$

C* 50 mM Tris pH7.8, 5 mM $MnCl_2$

1* 17.8 mg/ml PDE beads

2* 17.8 mg/ml PDE beads + 200 mM $ZnCl_2$

The compounds of the invention are generally selective for PDE10 compared to other PDEs and there are a few that also have affinity for PDE1B1, 4D3 and 5A3. Table 4 provides data of some compounds according to the invention.

Apomorphine-induced Stereotypy in Rats (APO)

Apomorphine (1.0 mg/kg, i.v.)-induced stereotypy (compulsive sniffing, licking, chewing) was scored every 5 min over the first hour after injection of apomorphine, following a 1 hour interval pre-treatment with the test compound. The score system was: (3) pronounced, (2) moderate, (1) slight, and (0) absent.Criteria for drug-induced inhibition of stereotypy: fewer than 6 scores of 3 (0.16% false positives), fewer than 6 scores of ≥ 2 (0.0% false positives), or fewer than 7 scores of ≥ 1 (0.81% false positives).

PDE10 Occupancy

Dose-response or single dose experiments were performed to measure PDE10 occupancy 1 hour after subcutaneous (s.c.) or oral (p.o.) administration. Male Wistar rats (200 g) were treated by s.c. or p.o. administration of various PDE10 inhibitors. The PDE10 radioligand [^{3}H]-MP-10 (10 µCi/animal) was injected intravenously (i.v.) 30 minutes before sacrifice. Brains were immediately removed from the skull and rapidly frozen. Twenty µm-thick brain sections were cut using a cryostat-microtome, thaw-mounted on microscope slides and loaded in a β-imager to quantify PDE10 occupancy in the striatum.

PCP-induced hyperlocomotion in rats

Apparatus

Motor activity [horizontal activity (locomotion) and vertical activity (rearing)] was recorded in male Wiga rats (body weight: 175-275 g; housed overnight in groups of 7 rats) using microprocessor-based activity monitors (MED Associates; length x width x height: 43.2 x 43.2 x 41.5 cm) over a period of 30 min. The resolution of the system was set at 100 msec. Total distance was defined as the distance traveled, measured by changes in the number or location of interrupted xy-beams (located in two arrays of 32 infrared light beams (1.25 cm apart) perpendicular to each other in a horizontal plane 2.0 cm above the floor). Vertical activity was defined as the number of periods of continuous breaks reported by an infrared array of 32 light beams in a horizontal plane 13 cm above the floor. The intensity of the light within the activity meters (measured in the centre at floor level) ranged between 110 and 130 LUX.

PCP-induced Hyperlocomotion in Rats

Male Wiga rats (200 to 260 g) were pretreated with test compound or solvent (10 ml/kg, s.c.) and placed in individual cages. At a predefined interval thereafter (60 min.), the rats were challenged with PCP (1.25 mg/kg, i.v.) and motor activity was measured over a period of 30 min starting immediately after the PCP challenge. The following all-or-none criteria were adopted for drug-induced effects: (1) inhibition (< 11000 counts; 2.9% false positives in 102 control rats), (2) blockade (< 500 counts; 0.0% false positives). The results of this test are shown in table 5 below.

Conditioned avoidance response (CAR) test

Apparatus

The apparatus consisted of an inner box surrounded by an outer box. The inner box was composed of four walls of transparent, synthetic material (length x width x height: 30 x 30 x 30 cm), an open top, and a grid floor made of 15 pairs of iron bars (2 mm diameter; 6 mm inter-bar distance). Odd and even bars were connected with a source of alternative current (1.0 mA; Coulbourn Instruments Solid State Shocker/Distributor), which could be interrupted by a switch. The outer box was composed of the same material (length x width x height: 40 x 40 x 36 cm), also with an open top, with a distance of 5 cm between the inner and outer box on all sides. To decrease the amount of environmental stimuli, three walls of the outer box were made non-transparent. The front wall was left transparent to allow the necessary inspection of the animal during the test. The upper edge of the outer and inner box served as a target for the rats on which to jump with fore- and hind-paws, respectively.

Avoidance Conditioning and Selection of Animals

From their arrival in the laboratory on the experimental day, male Wiga Wistar rats (230 ± 30 g) were housed in individual cages provided with bedding material. The rats received 5 training sessions at 15-min time intervals over a 1-h period during which, the rats were conditioned to avoid an electric shock: the rat was placed on the non-electrified grid floor and the grid was electrified 10 s later for not more than 30 s, if the rat did not jump out of the box. Only rats that showed correct avoidance responses in all the last 3 training sessions were included for further experiments, and received the test compound or solvent immediately after the last training session.

Experimental Sessions

The rats were tested 3 times, i.e. at 60, 90 and 120 min after the injection of test compound or solvent. Latency to avoidance was recorded. The median avoidance response obtained over the three experimental sessions for each rat were used for further calculations. A median avoidance latency > 8 s was selected as an all-or-none criterion for drug-induced inhibition of avoidance (occurring in only 1.5% of solvent-pretreated control rats; n = 66). The results of this test are shown in table 5 below.

SCH-23390-induced Hypolocomotion in Mice

SCH-23390 (0.08 mg/kg, i.v.)-induced hypolocomotion was evaluated over a 30-min period starting immediately after the SCH-23390 challenge in male NMRI mice pretreated 0.5 h earlier with test compound or solvent. Averaged activity in solvent-treated control mice was 1540 ± 559 counts (mean ± SD; n = 103). Criterion for drug-induced reversal of the SCH-23390-induced hypolocomotion: total distance: > 2500 counts (2.9% false positives in controls).

Object Recognition Test

Methods

Animals

60 female hooded-Lister rats (Charles River, UK) were used as subjects for these studies and weighed 248g ± 20g. Rats were allowed at least a 7-day acclimatization period to the animal unit prior to commencement of experimentation. Rats were housed in groups of 5 under standard laboratory conditions under a 12 h light:dark cycle, lights on at 0700 h. All testing was carried out in the light phase. Food and water were freely provided. All experiments were conducted in accordance with the Animals Scientific

Procedures Act, U.K. 1986 and were approved by the University of Bradford ethical review panel.

Treatment

40 mg of test compound was dissolved in 5 ml of 40% hydroxypropyl β-cyclodextrin (HPBC) solution. The solution was sonicated until completely dissolved. 2 ml of sterile water was added and the pH measured and adjusted with NaOH solution (0.1N) to obtain pH ~4. Finally, sterile water was added to a final volume of 10 ml. This stock solution was then diluted in 20% HPBC to obtain the final concentrations.

100 mg of PQ10 was dissolved in a 40% HPBC solution and 8 mg of tartaric acid. The solution was sonicated until completely dissolved. 5 ml of sterile water was added and the pH measured and adjusted with NaOH solution (0.1N) to obtain pH ~4. Finally sterile water was added to a final volume of 10 ml.

Test compound was administered at doses of 0.3 and 1.0 mg/kg via the oral route 30 min prior to testing.

PQ10 was administered at a dose of 1.0 mg/kg via the oral route 30 min prior to testing.

Object recognition memory

Certain pre-clinical tests allow the observation of relatively subtle cognitive deficits in the rat that resemble cognitive symptoms in subjects with schizophrenia. The cognitive deficits observed are seen in behaviours such as episodic memory, which can be measured by recognition tasks such as the novel object recognition (NOR) paradigm. A recognition memory task allows the comparison between presented stimuli and previously stored information. Ennaceur, A Delacour, J (1988) A new one-trial test for neurobiological studies of memory in rats Behav Brain Res 31: 47-59 described the NOR test in rats which was based on the differential exploration of familiar and new objects. The NOR test is a non-rewarded, ethologically relevant paradigm based on the spontaneous exploratory behaviour of rats that measures episodic memory. Each session consists of two trials. In the first trial, the rats are exposed to two identical objects in an open field. During the second trial, rats are exposed to two dissimilar objects, one familiar object from the first trial and one new object. Object recognition in rats can be measured as the difference in time spent exploring the familiar and the new object. Rats have been shown to spend more time exploring the new object. It was found that rats are able to discriminate between the familiar and the novel object when the inter-trial interval is between 3 minutes and 1-3 hours, but not when it is greater than 24 hours, although this effect may be sex dependent in the rat. The duration of each trial is also important as a preference for the novel object only lasts during the first

1 or 2 minutes, after which time preference diminishes as both objects become familiar and are explored equally.

Procedure

Allocation of Treatment groups

Rats were randomly assigned to the 8 treatment groups

Habituation

Rats were allowed to habituate to the empty test box and the behavioural test room environment for 1 h on day 1. Prior to behavioural testing on day 2 rats were given a further 3 min habituation.

Behavioural testing

Following the 3 min habituation period, the rats were given two 3 min trials (T1 and T2) which were separated by a 1 min inter-trial interval in the home cage during which the objects were changed.

T1=Trial 1, the acquisition trial

In this trial, the animals were allowed to explore two identical objects (A1 and A2) for 3 min.

T2=Trial 2, the retention trial

In this trial, the animals explored a familiar object (A) from T1 and a novel object (B) for 3 min. The familiar object presented during T2 was a duplicate of the object presented in T1 in order to avoid any olfactory trails.

Object exploration

The object exploration was defined by animals licking, sniffing or touching the object with the forepaws whilst sniffing, but not leaning against, turning around, standing or sitting on the object. The exploration time (s) of each object (A1, A2, A and B) in each trial were recorded using two stopwatches and the following factors were calculated.

Total exploration time of both objects in the acquisition trial (s).

Total exploration time of both objects in the retention trial (s).

Habituation of exploratory activity. The locomotor activity (LMA) included the exploration time, as measured by the number of lines crossed, for both the trials.

Discrimination index (DI), which was calculated as shown below:

$$\frac{\text{time spent exploring novel object – time spent exploring familiar object}}{\text{total time spent in exploring the objects}}$$

Behaviour in all trials was recorded on video for subsequent blind scoring.

Exclusion criteria

If an animal failed to explore one or both of the objects in the acquisition trial, that animal was not included in the final analysis, ie if exploration time was 0 seconds at either object in acquisition that animal was excluded.

Statistical analysis

All data are expressed as mean ± SEM, (n = 3 to 10 per group) and were analysed by a two way ANOVA (factors are: drug and exploration time of the two objects) or one way ANOVA (LMA and DI) with further analysis by a post-hoc student's t-test (time spent exploring objects in acquisition and retention trials) or Dunnett's t-test (LMA and DI). When student's t-test was used to analyse time spent exploring objects, significance was based upon the difference in time spent exploring the novel or familiar object, not in comparison to vehicle. For the discrimination index Dunnett's t-tests were used to compare values against PCP/Veh treated group, and against the Veh/Veh group, as appropriate. Results showed that sub-chronic PCP (2 mg/kg ip twice daily for 7 days followed by 7 days drug-free period) produced a selective cognitive deficit in the retention phase of the NOR task in female rats.

The effects of acute treatment with compound 1 (0.3-1.0 mg/kg) or the comparator PQ10, were selective for the retention phase of the NOR task.

Table 3. Pharmacological data for compounds according to the invention.

pIC_{50} corresponds to the –log IC_{50} expressed in mol/L.

ED_{50} is the dose at which 50% of the tested animals show the effect.

n.t. means not tested.

n.d. means the compound was found not active at 2.5 or at 10 mg/kg (the latter being indicated as (a)), taken as threshold value, and was not further tested.

* means the compound was not soluble and was tested orally as a suspension.

≤ means that the compound was found active in 60% of the animals at the indicated dose level; ≥ means that in 30% of the animals the compound was found active at the indicated dose level.

Co. No.	PDE10A2 pIC_{50}	APO ED_{50} (mg/kg)
141	8.00	n.d.*
10	7.94	1.2
50	7.84	0.8
142	7.84	5
46	7.76	n.d.
143	7.76	1.2
135	7.74	3.1*
5	7.72	n.d.
54	7.68	1.2
87	7.66	n.d.
124	7.65	1.2
6	7.63	n.d.
93	7.60	n.d.
105	7.60	n.d.
148	7.60	5
7	7.59	0.3
137	7.59	n.d.
3	7.58	0.8
20	7.56	n.d.
123	7.56	n.d.
38	7.54	n.d.
122	7.52	n.d.
26	7.51	n.d.
27	7.5	n.d.
25	7.47	n.d.*
131	7.46	3.1
115	7.45	n.d.*(a)
35	7.42	5
55	7.42	n.d.
138	7.40	n.d.*(a)
4	7.39	n.d.
29	7.36	$\geq$ 2.5
80	7.35	n.d.

Co. No.	PDE10A2 pIC_{50}	APO ED_{50} (mg/kg)
102	7.35	n.d.
44	7.34	n.d.
91	7.33	1.2
2	7.33	n.d.
37	7.30	1.5
45	7.30	n.d.
76	7.30	n.d.
118	7.30	$\leq$ 10*
126	7.30	n.d.
128	7.30	n.d.(a)
56	7.29	n.d.
83	7.29	n.d.
114	7.28	n.d.
146	7.28	n.t.
104	7.27	n.d.
17	7.26	n.d.*
95	7.26	n.d.*
22	7.25	0.5
36	7.25	5
1	7.24	1.3
92	7.24	n.d.
145	7.23	n.d.
31	7.22	n.d.
119	7.21	n.d.*(a)
106	7.18	n.d.
90	7.17	n.d.
147	7.17	5
139	7.16	n.d.*
39	7.15	n.d.
132	7.15	n.d.(a)
32	7.11	5
33	7.11	$\geq$ 2.5*
24	7.10	n.d.

Co. No.	PDE10A2 pIC_{50}	APO ED_{50} (mg/kg)
28	7.08	1.2
71	7.08	≥ 2.5*
125	7.08	≥ 2.5
67	7.06	n.d.(a)
47	7.04	n.d.
42	7.03	n.d.
133	7.02	3.1
73	7.01	n.d.
111	7.01	n.d.
117	7.01	n.t.
21	6.99	1.5
51	6.98	n.d.
134	6.98	5
19	6.97	5
98	6.96	n.d.
9	6.95	n.d.
23	6.95	n.d.
127	6.95	2.0
48	6.94	≥ 2.5
88	6.94	n.d.
34	6.93	n.d.
40	6.93	n.d.
14	6.92	n.d.
16	6.92	3.1
30	6.91	7.1
72	6.91	≥ 2.5*
78	6.91	n.d.
70	6.90	n.d.
77	6.89	n.d.
89	6.88	n.d.*
116	6.88	n.d.*(a)
63	6.87	n.d.(a)
97	6.85	n.d.

Co. No.	PDE10A2 pIC_{50}	APO ED_{50} (mg/kg)
82	6.84	n.d.
149	6.82	n.d.
21a	6.82	n.t.
108	6.81	n.d.
68	6.80	≥ 2.5*
113	6.80	n.d.
8	6.79	n.d.
65	6.79	n.d.(a)
18	6.77	5
140	6.76	n.d.(a)
66	6.75	n.d.(a)
101	6.75	n.d.
58	6.73	n.d.
96	6.73	n.d.
43	6.72	n.d.
60	6.72	n.d.
11	6.71	n.d.
13	6.71	n.d.
81	6.71	n.d.
49	6.68	n.d.
53	6.67	n.d.
130	6.66	n.d.*(a)
12	6.65	n.d.
59	6.63	n.d.
121	6.63	n.d.(a)
109	6.60	n.d.
62	6.59	n.d.*
103	6.59	n.d.
79	6.58	n.d.
86	6.58	n.d.
107	6.57	n.d.
15	6.52	n.d.*
99	6.52	n.d.

Co. No.	PDE10A2 pIC_{50}	APO ED_{50} (mg/kg)
69	6.49	n.d.
144	6.49	n.t.
110	6.48	n.t.
61	6.47	1.2
84	6.43	n.t.
94	6.42	n.t.
41	6.39	n.d.
57	6.37	n.t.
112	6.37	n.t.
75	6.35	n.t.

Co. No.	PDE10A2 pIC_{50}	APO ED_{50} (mg/kg)
52	6.33	n.d.
64	6.32	n.d.*
136	6.28	n.t.
74	6.23	n.t.
85	6.18	n.t.
120	6.16	n.d.(a)
100	6.14	n.t.
129	5.58	n.t.
150	n.t.	n.t.

Table 4. *In vitro* selectivity of compounds according to the invention (expressed as pIC_{50}).

Co. No.	PDE 10A2	PDE 11A4	PDE 1B1	PDE 2A	PDE 3A	PDE 4D3	PDE 5A3	PDE 6AB	PDE 7A	PDE 8A1	PDE 9A
10	7.94	5.85	n.t.	5.18	<5	5.9	5.89	n.t.	<5	n.t.	<5
50	7.84	n.t.	n.t.	5.16	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
142	7.84	5.74	n.t.	5.26	5.29	5.55	5.94	n.t.	5.3	n.t.	<5
143	7.76	5.71	n.t.	5.4	5.84	5.29	6.19	n.t.	5.23	n.t.	<5
135	7.74	5.23	n.t.	<5	5.13	<5	5.59	n.t.	<5	n.t.	<5
54	7.68	n.t.	n.t.	<5	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
124	7.65	5.27	n.t.	5.06	5.16	5.13	5.71	n.t.	5.27	n.t.	<5
148	7.6	5.72	n.t.	5.36	5.5	5.59	5.91	n.t.	5.54	n.t.	<5
7	7.59	n.t.	n.t.	<5	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
3	7.58	<5	n.t.	<5	<5	<5	5.1	n.t.	<5	n.t.	<5
131	7.46	<5	n.t.	<5	<5	<5	5.07	n.t.	<5	n.t.	<5
35	7.42	<5	n.t.	<5	5.13	<5	<5	n.t.	<5	n.t.	<5
29	7.36	<5	n.t.	5.92	<5	<5	5.35	n.t.	<5	n.t.	<5
91	7.33	<5	n.t.	<5	<5	<5	5.07	n.t.	<5	n.t.	<5
37	7.3	4.4	n.t.	4.27	4.96	4.51	5.22	n.t.	4.34	n.t.	<4

Co. No.	PDE 10A2	PDE 11A4	PDE 1B1	PDE 2A	PDE 3A	PDE 4D3	PDE 5A3	PDE 6AB	PDE 7A	PDE 8A1	PDE 9A
118	7.3	<5	n.t.	<5	<5	<5	5	n.t.	<5	n.t.	<5
146	7.28	<5	n.t.	<5	<5	<5	5.72	n.t.	5.07	n.t.	<5
1	7.24	4.13	5.28	4.4	4.01	4.51	4.77	4.07	4.16	4.11	<4
22	7.25	5.17	n.t.	5.23	<4.3	5.56	5.46	n.t.	4.55	n.t.	<4.3
36	7.25	<5	n.t.	<5	<5	<5	<5	<5	<5	<5	<5
147	7.17	5.42	n.t.	<5	<5	5.42	5.93	n.t.	5.45	n.t.	<5
32	7.11	<5	n.t.	<5	<5	<5	<5	n.t.	<5	n.t.	<5
33	7.11	<5	n.t.	<5	<5	<5	<5	n.t.	<5	n.t.	<5
28	7.08	4.52	n.t.	4.57	4.52	4.88	4.86	n.t.	4.59	n.t.	<4
71	7.08	n.t.	n.t.	5.64	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
125	7.08	5.35	n.t.	5.07	<5	5.68	5.9	n.t.	<5	n.t.	<5
133	7.02	<5	n.t.	<5	<5	<5	5.62	n.t.	<5	n.t.	<5
117	7.01	5	n.t.	<5	<5	<5	<5	n.t.	<5	n.t.	<5
21	6.99	<4.3	n.t.	4.32	<4.3	4.55	4.72	n.t.	<4.3	n.t.	<4.3
30	6.91	<5	n.t.	<5	<5	<5	<5	n.t.	<5	n.t.	<5
134	6.98	5.27	n.t.	5.09	<5	5.26	6.23	n.t.	5.31	n.t.	<5
19	6.97	<5	n.t.	<5	<5	<5	<5	n.t.	<5	n.t.	<5
127	6.95	<5	n.t.	<5	<5	<5	5.33	n.t.	<5	n.t.	<5
48	6.94	n.t.	n.t.	<5	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
16	6.92	<5	n.t.	<5	<5	<5	<5	n.t.	<5	n.t.	<5
72	6.91	n.t.	n.t.	5.98	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
68	6.8	n.t.	n.t.	<5	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
18	6.77	<5	n.t.	<5	<5	<5	5	n.t.	<5	n.t.	<5
144	6.49	n.t.	n.t.	<5	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
110	6.48	n.t.	n.t.	<5	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
61	6.47	<5	<5	5.1	<5	<5	5.57	n.t.	<5	n.t.	<5
84	6.43	n.t.	n.t.	<5	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
94	6.42	n.t.	n.t.	<5	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
57	6.37	n.t.	n.t.	<5	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
112	6.37	n.t.	n.t.	5.09	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.

Co. No.	PDE 10A2	PDE 11A4	PDE 1B1	PDE 2A	PDE 3A	PDE 4D3	PDE 5A3	PDE 6AB	PDE 7A	PDE 8A1	PDE 9A
75	6.35	n.t.	n.t.	<5	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
136	6.28	n.t.	n.t.	<5	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
74	6.23	n.t.	n.t.	<5	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
85	6.18	n.t.	n.t.	<5	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
100	6.14	n.t.	n.t.	<5	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
129	5.58	n.t.	n.t.	<5	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.

Table 5. Pharmacological data for compounds according to the invention in the occupancy test.

Occ. means occupancy; ED_{50} means effective dose; SD means single dose; DR means dose response; sc means subcutaneous administration; po means *per os*, oral administration; * the data between brackets means the % occupancy at the highest dose tested.

Co. No.	PDE10 *in vivo* Occ.	ED_{50} sc (mg/kg)	ED_{50} po (mg/kg)	SD sc % occupancy at 10 mg/kg	SD po % occupancy at 10 mg/kg
1	DR sc and po	0.48	1.4	76%	n.t.
3	DR sc	2.0	n.t.	n.t.	n.t.
7	DR sc	1.6	n.t.	n.t.	n.t.
16	SD sc	n.t.	n.t.	52%	n.t.
18	SD sc	n.t.	n.t.	46%	n.t.
19	SD sc	n.t.	n.t.	57%	n.t.
21	DR sc and po	2.6	14	61%	n.t.
22	DR sc	0.94	n.t.	n.t.	n.t.
28	DR sc	1.1	n.t.	n.t.	n.t.
30	DR sc	>10 (6%)*	n.t.	n.t.	n.t.
35	SD sc	n.t.	n.t.	67%	n.t.
37	DR sc	2.2	n.t.	67%	n.t.
48	DR po	n.t.	4.3	n.t.	n.t.
62	SD po	n.t.	n.t.	n.t.	38%
65	SD sc	n.t.	n.t.	17%	n.t.
66	SD sc	n.t.	n.t.	29%	n.t.
67	SD sc	n.t.	n.t.	1%	n.t.

Co. No.	PDE10 *in vivo* Occ.	ED_{50} sc (mg/kg)	ED_{50} po (mg/kg)	SD sc % occupancy at 10 mg/kg	SD po % occupancy at 10 mg/kg
114	SD sc	n.t.	n.t.	72%	n.t.
118	SD po	n.t.	n.t.	n.t.	4%
121	SD sc	n.t.	n.t.	0%	n.t.
124	DR sc	3.0	n.t.	n.t.	n.t.
125	DR sc	>10 (42%)*	n.t.	n.t.	n.t.
127	SD sc	n.t.	n.t.	4%	n.t.
128	SD sc	n.t.	n.t.	40%	n.t.
130	SD po	n.t.	n.t.	n.t.	6%
131	SD sc	n.t.	n.t.	59%	n.t.
132	SD sc	n.t.	n.t.	44%	n.t.
137	SD po	n.t.	n.t.	n.t.	12%
138	SD po	n.t.	n.t.	n.t.	11%
140	SD po	n.t.	n.t.	n.t.	0%
142	SD sc	n.t.	n.t.	78%	n.t.
147	SD sc	n.t.	n.t.	22%	n.t.
148	SD sc	n.t.	n.t.	66%	n.t.
21a	DR sc and po	2.6	14	61%	n.t.

Table 6. Pharmacological data for compounds according to the invention in the PCP, CAR and SCH-23390 tests.

Co. No.	PCP ED_{50} (mg/kg)	CAR ED_{50} (mg/kg)	SCH-23390 ED_{50} (mg/kg)
1	2.0	4.7	7.1
21	6.1	5.4	5

Table 7. Effects of compound 1 on short-term memory.

Day 1: The ability of acute treatment with compound 1 (0.3-1.0 mg/kg, p.o) or PQ10 (1 mg/kg, p.o) to reverse the effect of sub-chronic PCP (2 mg/kg, i.p twice daily for seven days) on the exploration time (s) during the retention trial (T2) of a familiar object and a novel object in the 3 min retention trial in female rats.

	Vehicle + 20% HPBCD	PCP + 20% HPBCD	PCP + co. no. 1 (0.3 mg/kg)	PCP + co. no. 1 (1.0 mg/kg)	PCP + PQ10 (1 mg/kg)
T2(A) (seconds)	7.5 (± 1.4395)	17.5 (± 2.1042)	11.8 (± 2.6709)	10.7 (± 1.8622)	7.9 (± 1.6017)

	Vehicle + 20% HPBCD	PCP + 20% HPBCD	PCP + co. no. 1 (0.3 mg/kg)	PCP + co. no. 1 (1.0 mg/kg)	PCP + PQ10 (1 mg/kg)
T2(B) (seconds)	19.9 (± 3.6346)**	17.4 (± 2.2716)	17.6 (±2.7899)*	22.3 (±3.2251)**	19.9 (± 3.247)**
DI	0.3748 (± 0.1695)	-0.005 (± 0.0357)	0.3014 (± 0.1405)	0.3335 (± 0.0804)	0.4193 (± 0.0772)
LMA (no. of lines crossed)	62.8 (± 4.567518)	69.5 (± 5.647517)	56.5 (± 6.107503)	56.4 (± 7.212951)	65.5 (± 5.518152)

Data are expressed as the mean ± s.e.m (n=3-10 per group) and were analysed by ANOVA and post-hoc student's t-test. *P<0.05-**P<0.01; significant difference between time spent exploring the familiar (A) and novel (B) object. The difference in time exploring the novel and familiar object is analysed by student's t-test.

E. Prophetic composition examples

"Active ingredient" as used throughout these examples relates to a final compound of formula (I), the pharmaceutically acceptable salts thereof, the solvates and the stereochemically isomeric forms thereof.

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 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.

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 in water.

4. Ointment

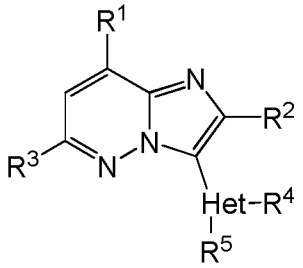
Active ingredient	5 to 1000 mg
Stearyl alcohol	3 g
Lanoline	5 g
White petroleum	15 g
Water	ad 100 g

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 of formula (I)



(I)

or a stereoisomeric form thereof, wherein

R^1 is pyridinyl; pyridinyl optionally substituted with halogen, C_{1-4}alkyl, trifluoromethyl or C_{1-4}alkyloxy; tetrahydropyranyl; or NR^6R^7;

R^2 is hydrogen, C_{1-4}alkyl, trifluoromethyl, C_{3-8}cycloalkyl, or C_{1-4}alkyloxy;

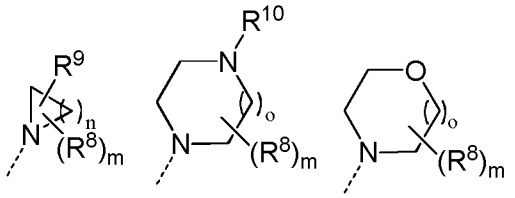
R^3 is hydrogen, chloro, C_{1-4}alkyl, trifluoromethyl, or C_{3-8}cycloalkyl;

Het is a 5- or 6- membered heterocyclic ring selected from the group consisting of pyridinyl, pyrimidinyl, pyridazinyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isothiazolyl, isoxazolyl, oxadiazolyl and triazolyl;

R^4 is hydrogen, C_{1-4}alkyl, trifluoromethylC_{0-4}alkyl, hydroxyC_{1-4}alkyl, difluorocyclopropylmethyl, cyclopropyldifluoroethyl, C_{3-8}cycloalkyl, C_{1-4}alkyloxyC_{1-5}alkyl, C_{1-4}alkyloxy, trifluoromethylC_{0-4}alkyloxy, C_{3-8}cycloalkylC_{1-4}alkyloxy, C_{3-8}cycloalkylC_{1-4}alkyl, C_{1-6}alkyloxyC_{1-4}alkyloxy, tetrahydropyranyl, pyridinylmethyl, $NR^{6a}R^{7a}C_{1-4}$alkyl or $NR^{6a}R^{7a}$;

R^5 is hydrogen or C_{1-4}alkyl;

R^6, R^{6a}, R^7 and R^{7a} are each independently hydrogen or C_{1-4}alkyl, or taken together with N can be a radical of Formula (a), (b) or (c)



(a) **(b)** **(c) ;**

wherein

each R^8, if present, independently of one another is C_{1-4}alkyl ;

R^9 is hydrogen or C_{1-4}alkyloxy ;

R^{10} is hydrogen or C_{1-4}alkyl;

m is 0, 1, 2, 3, 4 or 5;

n is 2, 3, 4, 5 or 6;

o is 1 or 2 ;

or a pharmaceutically acceptable salt or a solvate thereof.

2. The compound according to claim 1, or a stereoisomeric form thereof, wherein R^1 is selected from pyridinyl; pyridinyl optionally substituted with halogen, C_{1-4}alkyl, trifluoromethyl or C_{1-4}alkyloxy; tetrahydropyranyl; and NR^6R^7; wherein R^6 and R^7 taken together with the nitrogen can be a radical of Formula (a), (b) or (c) as defined in claim 1;

R^2 is selected from hydrogen, methyl, ethyl, cyclopropyl, isopropyl, methoxy and trifluoromethyl ;

R^3 is selected from hydrogen, chloro, methyl, trifluoromethyl and cyclopropyl ; and

Het is selected from the group consisting of pyridinyl, pyrimidinyl, pyridazinyl, oxazolyl, thiazolyl, pyrazolyl, isothiazolyl, isoxazolyl, oxadiazolyl and triazolyl ;

or a pharmaceutically acceptable salt or a solvate thereof.

3. The compound according to claim 1 or 2, or a stereoisomeric form thereof, wherein

R^1 is selected from pyridinyl which may be optionally substituted with halogen, C_{1-4}alkyl, trifluoromethyl or C_{1-4}alkyloxy; morpholinyl; and NR^6R^7; wherein R^6 and R^7 taken together with the nitrogen can be a radical of Formula (a) or (c) wherein n is 3 and o is 1;

Het is selected from pyridinyl and pyrazolyl;

R^4 is hydrogen, C_{1-4}alkyl, trifluoromethylC_{0-4}alkyl, hydroxyC_{1-4}alkyl, difluorocyclopropylmethyl, cyclopropyldifluoroethyl, C_{3-8}cycloalkyl, C_{1-4}alkyloxyC_{1-5}alkyl, C_{1-4}alkyloxy, trifluoromethylC_{0-4}alkyloxy,

C_{3-8}cycloalkylC_{1-4}alkyloxy, C_{1-6}alkyloxyC_{1-4}alkyloxy, tetrahydropyranyl, pyridinylmethyl, $NR^{6a}R^{7a}C_{1-4}$alkyl or $NR^{6a}R^{7a}$;

wherein R^6, R^{6a}, R^7 and R^{7a} are each independently hydrogen or C_{1-4}alkyl, or taken together with the nitrogen can be a radical of formula (a), (b) or (c), wherein n is 3, R^9 is hydrogen or C_{1-4}alkyloxy, m is 0, o is 1 and R^{10} is hydrogen;

or a pharmaceutically acceptable salt or a solvate thereof.

4. The compound according to claim 1 or 2, or a stereoisomeric form thereof, wherein

R^1 is selected from morpholinyl and pyridinyl ;

R^2 is selected from hydrogen, methyl, ethyl, methoxy, and cyclopropyl ;

R^3 is selected from hydrogen, methyl, and cyclopropyl ;

Het is pyridinyl or pyrazolyl ;

R^4 is selected from ethyl; isopropyl; isobutyl; 2,2,2-trifluoroethyl; 2-hydroxy-2-methylpropyl; 2,2-difluoro-2-cyclopropylethyl; cyclopropyl; 2-methoxyethyl; (2*S*)-2-methoxypropyl; 2-ethoxyethyl; ethoxymethyl; 1-ethoxy-1-methylethyl; 1-methoxy-1-methylethyl; 2-methoxy-1,1-dimethylethyl; 3-methoxy-3-methylbutyl; 3-methoxypropyl; 2-methoxy-2-methyl-propyl; 2-methoxyethoxy; 2-methoxy-2-methyl-propoxy; tetrahydro-*2H*-pyran-4-yl; morpholin-4-yl; piperazin-1-yl; and (3*R*)-3-methoxypyrrolidin-1-yl;

and R^5 is hydrogen or methyl ;

or a pharmaceutically acceptable salt or a solvate thereof.

5. The compound according to claim 1 or 2, or a stereoisomeric form thereof, wherein

R^1 is selected from morpholin-4-yl, pyridin-3-yl and pyridin-4-yl ; and

Het is selected from pyridin-3-yl, pyridin-4-yl and *1H*-pyrazol-4-yl ;

or a pharmaceutically acceptable salt or a solvate thereof.

6. The compound according to claim 1 or 2, or a stereoisomeric form thereof, wherein

R^1 is selected from morpholin-4-yl ; and

Het is pyridin-3-yl or pyridin-4-yl ;

or a pharmaceutically acceptable salt or a solvate thereof.

7. The compound according to claim 1, or a stereoisomeric form thereof, wherein

R^1 is morpholin-4-yl ;

R^2 is methyl ;
R^3 is hydrogen ;
Het is pyridin-3-yl ;
R^4 is 2-methoxyethyl ; and
R^5 is hydrogen ;
or a pharmaceutically acceptable salt or a solvate thereof.

8. The compound of formula (I) according to claim 1, selected from the group consisting of

3-[6-(2-methoxyethyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 1),
3-[6-(2-methoxyethyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine hydrochloride (compound 1a),
3-[6-(2-methoxyethyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine maleate (compound 1b),
3-[6-(2-methoxyethyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine monohydrate (compound 1c),
3-[6-(3-methoxypropyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 2),
3-[6-(2-methoxy-2-methylpropyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 3),
3-[6-(2-methoxy-1,1-dimethylethyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 4),
3-[6-(1-ethoxy-1-methylethyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 5),
3-[6-(1-methoxy-1-methylethyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 6),
3-[6-(2-methoxy-2-methylpropyl)-3-pyridinyl]-2-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 7),
3-[6-(2-methoxyethoxy)-5-methyl-3-pyridinyl]-2-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 8),
3-[6-(2-methoxyethoxy)-3-pyridinyl]-2-methyl-8-(3-pyridinyl)-imidazo[1,2-b]pyridazine (compound 9),
2-cyclopropyl-3-[6-(2-methoxyethyl)-3-pyridinyl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 10),
3-[6-(2-methoxyethyl)-3-pyridinyl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 11),
2-methoxy-3-[6-(2-methoxyethyl)-3-pyridinyl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 12),

6-cyclopropyl-3-[6-(2-methoxyethyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 13),
6-cyclopropyl-3-[6-(2-methoxyethyl)-3-pyridinyl]-2-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 14),
2-cyclopropyl-3-[6-(2-methoxyethyl)-3-pyridinyl]-6-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 15),
3-[6-(2-methoxyethoxy)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 16),
3-[6-(ethoxymethyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 17),
3-[6-(2-methoxy-2-methylpropoxy)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 18),
2-methyl-8-(4-morpholinyl)-3-[6-(4-morpholinyl)-3-pyridinyl]-imidazo[1,2-b]pyridazine (compound 19),
3-[6-(2-methoxyethyl)-3-pyridinyl]-2-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 20),
3-[6-(2-methoxyethoxy)-3-pyridinyl]-2-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 21),
3-[6-(2-methoxyethoxy)-3-pyridinyl]-2-methyl-8-(4-pyridinyl)-imidazo[1,2-*b*]pyridazine hydrochloride (compound 21a),
2-cyclopropyl-3-[6-(2-methoxyethyl)-3-pyridinyl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 22),
3-[6-(2-methoxyethyl)-3-pyridinyl]-2,6-dimethyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 23),
3-[6-(2-methoxyethyl)-3-pyridinyl]-2,6-dimethyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 24),
3-[6-(2-ethoxyethyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 25),
3-[2-(2-methoxyethyl)-4-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 26),
2-methyl-8-(4-morpholinyl)-3-[6-(tetrahydro-*2H*-pyran-4-yl)-3-pyridinyl]-imidazo[1,2-b]pyridazine (compound 27),
3-(6-ethyl-3-pyridinyl)-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 28),
3-[6-(3-methoxy-3-methylbutyl)-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 29),
2-methyl-8-(4-morpholinyl)-3-[6-(1-piperazinyl)-3-pyridinyl]-imidazo[1,2-b]pyridazine (compound 30),
2-methyl-3-[6-(4-morpholinyl)-3-pyridinyl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 31),

2-methyl-3-[6-(1-methylethyl)-3-pyridinyl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 32),
3-(6-cyclopropyl-3-pyridinyl)-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 33),
3-[6-[(3*R*)-3-methoxy-1-pyrrolidinyl]-3-pyridinyl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 34),
2-methyl-3-[1-(2-methylpropyl)-*1H*-pyrazol-4-yl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 35),
3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 36),
3-[1-(2-methoxy-2-methylpropyl)-*1H*-pyrazol-4-yl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 37),
2-cyclopropyl-3-[1-(2-methoxy-2-methylpropyl)-*1H*-pyrazol-4-yl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 38),
2-cyclopropyl-3-[6-(2-methoxy-2-methylpropyl)-3-pyridinyl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine hydrochloride (compound 45a),
2-cyclopropyl-3-[6-(2-methoxy-2-methylpropyl)-3-pyridinyl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 45),
3-[6-(2-methoxy-2-methylpropyl)-3-pyridinyl]-2,6-dimethyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 48),
2-cyclopropyl-3-[6-(2-methoxy-2-methylpropyl)-3-pyridinyl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 50),
5-[2-cyclopropyl-8-(4-morpholinyl)imidazo[1,2-b]pyridazin-3-yl]-α,α-dimethyl-2-pyridineethanol (compound 54),
3-[6-(4-morpholinyl)-3-pyridinyl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 61),
2,6-dimethyl-8-(4-morpholinyl)-3-[6-(4-morpholinyl)-3-pyridinyl]-imidazo[1,2-b]pyridazine (compound 68),
2-cyclopropyl-6-methyl-3-[6-(4-morpholinyl)-3-pyridinyl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 71),
2-cyclopropyl-3-[6-(2-methoxyethoxy)-3-pyridinyl]-6-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 72),
2-methyl-8-(4-morpholinyl)-3-[2-(4-morpholinyl)-4-pyridinyl]-imidazo[1,2-b]pyridazine (compound 91),
3-{1-[(2,2-difluorocyclopropyl)methyl]-*1H*-pyrazol-4-yl}-2-methyl-8-morpholin-4-ylimidazo[1,2-*b*]pyridazine (compound 118),
2-methyl-3-[1-(2-methylpropyl)-*1H*-pyrazol-4-yl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 124),
6-cyclopropyl-3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 125),

2-ethyl-3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 127),
3-[1-[(2S)-2-methoxypropyl]-*1H*-pyrazol-4-yl]-2-methyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 131),
3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-2,6-dimethyl-8-(4-morpholinyl)-imidazo[1,2-b]pyridazine (compound 133),
3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-2,6-dimethyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 134),
2-methyl-8-(4-pyridinyl)-3-[1-(2,2,2-trifluoroethyl)-*1H*-pyrazol-4-yl]-imidazo[1,2-b]pyridazine (compound 135),
2-cyclopropyl-3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 142),
2-cyclopropyl-3-[1-(2-methoxy-2-methylpropyl)-*1H*-pyrazol-4-yl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 143),
6-chloro-3-[1-(2-methoxyethyl)-*1H*-pyrazol-4-yl]-2-methyl-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 147), and
2-cyclopropyl-3-[1-(2-methylpropyl)-*1H*-pyrazol-4-yl]-8-(4-pyridinyl)-imidazo[1,2-b]pyridazine (compound 148),

and the stereoisomeric forms, the pharmaceutically acceptable salts and the solvates thereof.

9. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1 to 8 and a pharmaceutically acceptable carrier or excipient.

10. A compound according to any one of claims 1 to 8 for use as a medicament.

11. A compound according to any one of claims 1 to 8 or a pharmaceutical composition according to claim 9 for use in the treatment or prevention of a central nervous system disorder selected from the group of psychotic disorders; drug induced psychosis; anxiety disorders; movement disorders; mood disorders; neurodegenerative disorders; disorders or conditions comprising as a symptom a deficiency in attention and/or cognition; drug addiction disorders; pain and metabolic disorders.

12. The compound according to claim 11, wherein the psychotic disorder is selected from the group consisting of schizophrenia, delusional disorder, schizoaffective disorder, schizophreniform disorder and substance-induced psychotic disorder.

13. A compound according to any one of claims 1 to 8 in combination with an additional pharmaceutical agent for use in the treatment or prevention of a condition as cited in any one of claims 11 to 12.

14. A process for preparing a pharmaceutical composition as defined in claim 9, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as defined in any one of claims 1 to 8.

15. A product comprising

(a) a compound as defined in any one of claims 1 to 8; and

(b) an additional pharmaceutical agent,

as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of a condition as cited in any one of claims 11 to 12.