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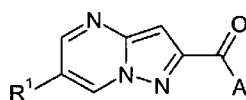
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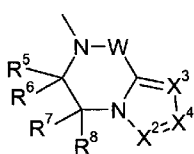
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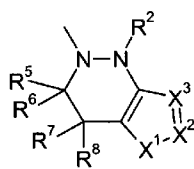
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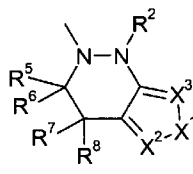
(I)



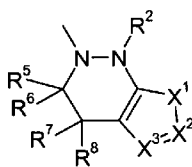
(a)



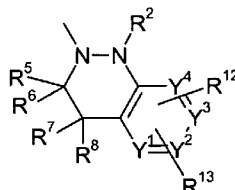
(b)



(c)



(d)



(e)

(57) Abstract: The invention relates to pyrazolopyrimidine derivatives of Formula (I) wherein R^1 represents chloro or bromo; A represents (a); (b); (c); (d); or (e), as well as their pharmaceutically acceptable salts. The invention further relates to a process for the preparation of such compounds. The compounds of the invention are mGluR5 modulators and are therefore useful for the control and prevention of acute and/or chronic neurological disorders.



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PYRAZOLOPYRIMIDINES, A PROCESS FOR THEIR PREPARATION AND THEIR USE AS MEDICINE

FIELD OF THE INVENTION

The present invention relates to Pyrazolopyrimidine derivatives, which can act as novel metabotropic glutamate receptor (mGluR) modulators, methods for their synthesis and their use as a medicament for the treatment of various diseases and/or prevention of disorders, e. g. neurological disorders, by administration of such substances.

BACKGROUND OF THE INVENTION

Neuronal stimuli are transmitted by the central nervous system (CNS) through the interaction of a neurotransmitter released by a neuron, which neurotransmitter has a specific effect on a neuroreceptor of another neuron. L-glutamic acid is considered to be a major excitatory neurotransmitter in the mammalian CNS, consequently playing a critical role in a large number of physiological processes. Glutamate-dependent stimulus receptors are divided into two main groups. The first group comprises ligand-controlled ion channels whereas the other comprises metabotropic glutamate receptors (mGluR). Metabotropic glutamate receptors are a subfamily of G-protein-coupled receptors (GPCR). There is increasing evidence for a peripheral role of both ionotropic and metabotropic glutamate receptors outside the CNS e.g. in chronic pain states.

At present, eight different members of these mGluRs are known. On the basis of structural parameters such as sequence homology, the second messenger system utilized by these receptors and their different affinity to low-molecular weight compounds, these eight receptors can be divided into three groups. mGluR1 and mGluR5 belong to Group I which are positively coupled to phospholipase C and their activation leads to a mobilization of intracellular calcium ions. mGluR2 and

mGluR3 belong to Group II and mGluR4, mGluR6, mGluR7 and mGluR8 belong to Group III, both of which are negatively coupled to adenylyl cyclase, i.e., their activation causes a reduction in second messenger cAMP and thus a dampening of neuronal activity.

The mGluR5 modulators have been shown to modulate the effects of the presynaptically released neurotransmitter glutamate via postsynaptic mechanisms. Moreover, as these modulators can be both positive and/or negative mGluR5 modulators, such modulators may increase or inhibit the effects mediated through these metabotropic glutamate receptors.

Of particular interest are those modulators which are negative mGluR5 modulators. Such modulators decrease the effects mediated through metabotropic glutamate receptors. Since a variety of patho-physiological processes and disease states affecting the CNS are thought to be related to abnormal glutamate neurotransmission, and mGluR5 receptors are shown to be expressed in many areas of the CNS and in PNS (peripheral nervous system), modulators of these receptors could be therapeutically beneficial in the treatment of diseases involving CNS and PNS.

Therefore, mGluR5 positive or negative modulators may be administered to provide neuroprotection and/or disease modification in the following acute or chronic pathological conditions or to provide a symptomatological effect on the following conditions:

Alzheimer's disease, Creutzfeld-Jakob's syndrome/disease, bovine spongiform encephalopathy (BSE), prion related infections, diseases involving mitochondrial dysfunction, diseases involving β -amyloid and/or tauopathy, Down's syndrome, hepatic encephalopathy, Huntington's disease, motor neuron diseases, amyotrophic lateral sclerosis (ALS), olivoponto-cerebellar atrophy, post-operative cognitive deficit (POCD), systemic lupus erythematosus, systemic sclerosis, Sjogren's syndrome, Neuronal Ceroid Lipofuscinosis, neurodegenerative cerebellar ataxias, Parkinson's disease, Parkinson's dementia, mild cognitive impairment, cognitive

deficits in various forms of mild cognitive impairment, cognitive deficits in various forms of dementia, dementia pugilistica, vascular and frontal lobe dementia, cognitive impairment, learning impairment, eye injuries, eye diseases, eye disorders, glaucoma, retinopathy, macular degeneration, head or brain or spinal cord injuries, head or brain or spinal cord trauma, trauma, hypoglycaemia, hypoxia, perinatal hypoxia, ischaemia, ischaemia resulting from cardiac arrest or stroke or bypass operations or transplants, convulsions, epileptic convulsions, epilepsy, temporal lobe epilepsy, myoclonic epilepsy, inner ear insult, inner ear insult in tinnitus, tinnitus, sound- or drug-induced inner ear insult, sound- or drug-induced tinnitus, hyperacusis, L-dopa-induced dyskinesias, L-dopa-induced dyskinesias in Parkinson's disease therapy, dyskinesias, dyskinesia in Huntington's disease, drug induced dyskinesias, neuroleptic-induced dyskinesias, haloperidol-induced dyskinesias, dopaminomimetic-induced dyskinesias, chorea, Huntington's chorea, athetosis, dystonia, stereotypy, ballism, tardive dyskinesias, neuroleptics-induced dyskinesia, tic disorder, torticollis spasmodicus, blepharospasm, focal and generalized dystonia, nystagmus, hereditary cerebellar ataxias, corticobasal degeneration, tremor, essential tremor, abuse, addiction, nicotine addiction, nicotine abuse, alcohol addiction, alcohol abuse, opiate addiction, opiate abuse, cocaine addiction, cocaine abuse, amphetamine addiction, amphetamine abuse, anxiety disorders, panic disorders, anxiety and panic disorders, social anxiety disorder (SAD), attention deficit hyperactivity disorder (ADHD), attention deficit syndrome (ADS), restless leg syndrome (RLS), hyperactivity in children, autism, dementia, dementia in Alzheimer's disease, dementia in Korsakoff syndrome, Korsakoff syndrome, vascular dementia, dementia related to HIV infections, HIV-1 encephalopathy, AIDS encephalopathy, AIDS dementia complex, AIDS-related dementia, major depressive disorder, major depression, depression, depression resulting from Borna virus infection, major depression resulting from Borna virus infection, bipolar manic-depressive disorder, drug tolerance, drug tolerance to opioids, movement disorders, fragile-X syndrome, irritable bowel syndrome (IBS), migraine, multiple sclerosis (MS), muscle spasms, pain, chronic pain, acute pain, inflammatory pain, neuropathic pain, diabetic neuropathic pain (DNP), pain related to rheumatic arthritis, allodynia, hyperalgesia, nociceptive pain, cancer pain, posttraumatic stress disorder (PTSD), schizophrenia, positive or cognitive or negative symptoms of

schizophrenia, spasticity, Tourette's syndrome, urinary incontinence, vomiting, pruritic conditions, pruritis, sleep disorders, micturition disorders, neuromuscular disorder in the lower urinary tract, gastroesophageal reflux disease (GERD), gastrointestinal dysfunction, lower esophageal sphincter (LES) disease, functional gastrointestinal disorders, dyspepsia, regurgitation, respiratory tract infection, bulimia nervosa, chronic laryngitis, asthma, reflux-related asthma, lung disease, eating disorders, obesity, obesity-related disorders, obesity abuse, food addiction, binge eating disorders, agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, social phobia, phobic disorders, substance-induced anxiety disorder, delusional disorder, schizoaffective disorder, schizophreniform disorder, substance-induced psychotic disorder, delirium, diabetes, hyperammonemia and liver failure and sleep disturbances..

The mGluR5 negative or positive modulators may also be administered to provide inhibition of tumour cell growth, migration, invasion, adhesion and toxicity in the peripheral tissues, peripheral nervous system and CNS. MGlur5 modulators may be administered to provide therapeutic intervention in neoplasia, hyperplasia, dysplasia, cancer, carcinoma, sarcoma, oral cancer, squamous cell carcinoma (SCC), oral squamous cell carcinoma (SCC), lung cancer, lung adenocarcinoma, breast cancer, prostate cancer, gastric cancer, liver cancer, colon cancer, colorectal carcinoma, rhabdomyosarcoma, brain tumour, tumour of a nerve tissue, glioma, malignant glioma, astrogloma, neurogloma, neuroblastoma, glioblastoma, medulloblastoma, cancer of skin cells, melanoma, malignant melanoma, epithelial neoplasm, lymphoma, myeloma, Hodgkin's disease, Burkitt's lymphoma, leukemia, thymoma, and other tumours.

The mGluR5 positive or negative modulators may also be administered to provide disease modification an/or to provide a symptomatological effect on the following conditions: diabetes, hyperammonemia and liver failure.

Further indications for mGluR5 negative or positive modulators include those indications wherein a particular condition does not necessarily exist but wherein a

particular physiological parameter may be improved through administration of the instant compounds, for example cognitive enhancement, learning impairment and/or neuroprotection.

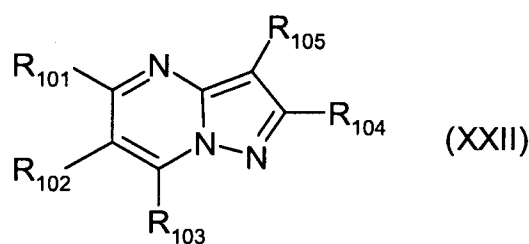
Positive modulators may be particularly useful in the treatment of positive and negative symptoms in schizophrenia and cognitive deficits in various forms of dementia and mild cognitive impairment.

In the literature, several types of modulators of mGluR5 have already been described.

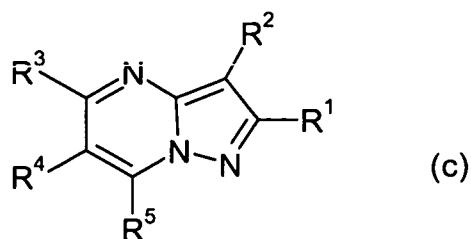
Furthermore, several types of pyrazolopyrimidine compounds have been disclosed in the prior art.

Various methods for preparing substituted pyrazolopyrimidine derivatives are known, e. g. from G. Hajos and Z. Riedl, Science of Synthesis 109, 613-678 (2002) and from Laura Bettinetti (Ph. D. Thesis, University of Erlangen, Germany, 2004).

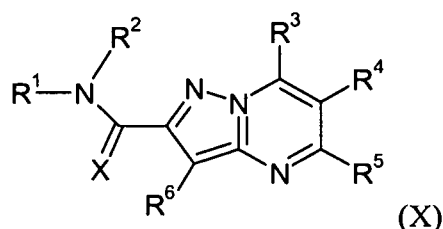
In WO 2004/087153 various pyrazolopyrimidines of formula (XXII) are described, which can act as small molecule immune potentiators (SMIP) and which can be used e.g. for cancer treatment.



Furthermore, in WO 2004/089471, the use of substituted pyrazolo[1,5-a]pyrimidines or prodrugs or salts thereof are described for the preparation of a pharmaceutical composition for the treatment of disorders and diseases where it is desirable to modulate the activity of the enzyme 11 β HSD1 or to inhibit 11 β HSD1. In the document WO 2004/089471, pyrazolo(1,5-a)pyrimidine derivatives of the following general formula (C) are disclosed:



In WO 2003/037900, further specific pyrazolopyrimidine compounds are described as inhibitors of ion-channels in human cells. In this document compounds having the following general formula (X) are described:



wherein

R¹ is e. g. alkyl; R² is e.g. hydrogen or alkyl; or

R¹ and R² taken together with the nitrogen atom to which they are optionally joined to form a 4- to 8-membered heterocycloaryl ring;

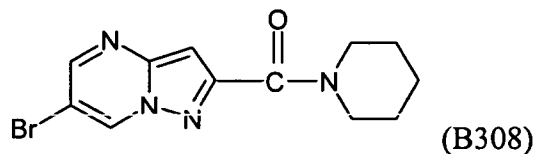
R³ is e.g. hydrogen, alkyl, halo, amino or aryl;

R⁴ is e.g. hydrogen, halo, alkyl or aryl; and

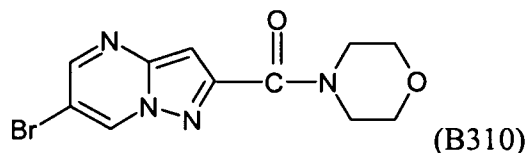
R⁵ is a member selected from substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl and substituted or unsubstituted heterocycloalkyl; R⁶ is e.g. hydrogen, halo or aryl; and

X is a member selected from O and S.

Several pyrazolopyrimidine compounds have been tested which are found to be not significantly active as inhibitors of ion-channels in human cells. In this document WO 2003/037900, compounds of the following two structures are mentioned as example compounds (B308) and (B310), which however have shown no particular activity as metabotropic glutamate receptor (mGluR5) modulators:

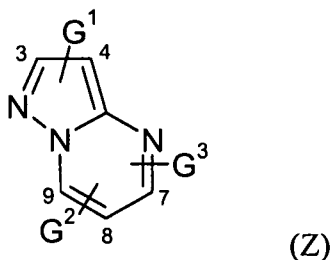


(6-Bromopyrazolo[1,5-a]pyrimidin-2-yl)-piperidin-1-yl-methanone



(6-Bromopyrazolo[1,5-a]pyrimidin-2-yl)-morpholin-4-yl-methanone.

In WO 2003/101993 several types of pyrazolopyrimidine compounds and their use for the treatment of hepatitis infections are disclosed. WO 2003/101993 deals with compounds of the following general formula (Z)



wherein:

G^1 is selected e.g. from the group of -OH, cyano, -C(O)-OH, -C(O)-NR²R³, where R² and R³ taken together from a 5- or 6-membered heteroaromatic or saturated or partially unsaturated heterocyclic ring, or

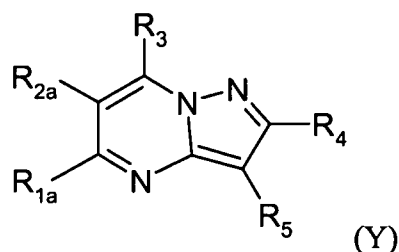
G^2 is independently are selected from the group consisting e.g. of alkyl, cycloalkyl, aryl, heteroaryl, saturated or partially unsaturated heterocyclic radical, trifluoromethyl,

G^3 can be absent or is independently selected from the group consisting of e.g. alkyl, cycloalkyl, aryl, heteroaryl, saturated or partially unsaturated heterocyclic radical,

G^2 and G^3 , collectively, are attached at any two of positions C7, C8 and C9 of the pyrimidine ring, the remaining position being optionally substituted with alkyl, alkenyl, alkynyl, halo, fluoroalkyl, hydroxyl, alkoxy, or cyano;

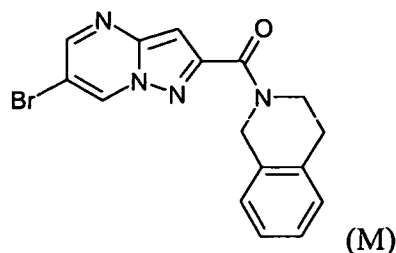
wherein the ring portion of any of said cycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, or heterocyclic radical in G^1 , G^2 or G^3 can be optionally substituted.

In WO 2003/091256 particular pyrazolopyrimidine derivatives which have a NADPH-oxidase inhibitor activity are described. The compounds have the following general formula (Y)



wherein R_{1a} , R_{2a} , R_3 - R_5 represent hydrogen, halogen, lower alkyl that may be substituted, lower alkenyl that may be substituted, lower alkynyl that may be substituted, cycloalkyl that may be substituted, cycloalkenyl that may be substituted, cycloalkynyl that may be substituted, aryl that may be substituted, heterocyclic group that may be substituted, hydroxyl, alkoxy that may be substituted, aryloxy that may be substituted, heterocyclic oxy that may be substituted, acyl that may be substituted, monosubstituted carbonyloxy that may be substituted, carbamoyl that may be substituted, diazo, amidino that may be substituted, azido, nitroso, nitro, amino that may be substituted, imino that may be substituted, cyano, mercapto, monosubstituted sulfinyl that may be substituted, monosubstituted sulfonyl that may be substituted, sulfo, or trisubstituted silyl, and any combinations of R_{1a} , R_{2a} , R_3 - R_5 may together form a ring structure.

A further pyrazolopyrimidine compound which has already been described in the literature (see ChemBridge Corporation; Registry Nr. 833441-66-0; of February 18, 2005), has the following structure (M):



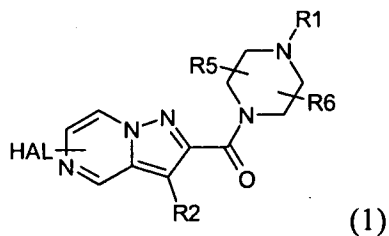
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,2,3,4-tetrahydro-isoquinolin-2-yl)-methanone.

This compound, however has only a limited activity as metabotropic glutamate receptor (mGluR5) modulator and furthermore is not selective.

In WO 2006/015737 further heterocyclic compounds which can contain a carboxylic acid amid function are disclosed which have an activity at dopamine receptors and which can be used for the treatment of CNS-diseases. As one example structure, pyrazolopyrimidines are mentioned.

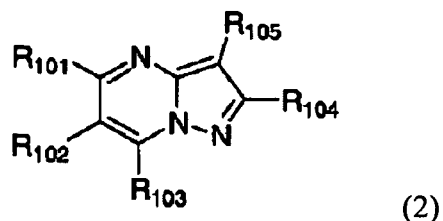
In WO 2002/088088 the synthesis of tetrahydro-isoquinolin compounds is disclosed which can serve as intermediates for the synthesis of pharmaceutically active compounds.

In WO 2005/009947 particular pyrazolopyrimidine derivatives which act as tubulin polymerization inhibitors are described. The compounds have the following general formula (1)



wherein R_1 and R_2 independently represent aryl, heteroaryl, wherein aryl and heteroaryl may be substituted.

In WO 2004/0087153 particular pyrazolopyrimidine derivatives which act as immunopotentiators are described. The compounds have the following general formula (2)



wherein R_{101} is e.g. hydrogen, halogen, amino, or nitro; R_{102} is e.g. hydrogen or halogen; R_{103} is e.g. hydrogen, nitro, or halogen; R_{104} is e.g. hydrogen, aryl, heteroaryl, or a carbocyclyl groups; R_{105} is e.g. hydrogen or substituted or unsubstituted aryl, wherein at least one R_{104} and R_{105} is not hydrogen.

THE PRESENT INVENTION

It now has been found that certain pyrazolopyrimidine derivatives which differ in structure from the known pyrazolopyrimidines, are potent mGluR5 modulators. Therefore, these substances may be therapeutically beneficial in the treatment of conditions which involve abnormal glutamate neurotransmission or in which modulation of mGluR5 receptors results in therapeutic benefit. These substances are preferably administered in the form of a pharmaceutical composition, wherein they are present together with one or more pharmaceutically acceptable diluents, carriers, or excipients.

OBJECTS OF THE INVENTION

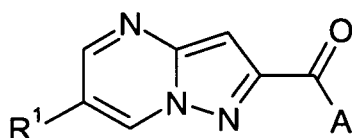
It is an object of the present invention to provide novel pharmaceutical compounds which are mGluR5 modulators and pharmaceutical compositions thereof. It is a further object of the invention to provide a novel method of treating, eliminating, alleviating, palliating, or ameliorating undesirable CNS disorders which involve abnormal glutamate neurotransmission by employing a compound of the invention or a pharmaceutical composition containing the same.

An additional object of the invention is the provision of processes for producing the pyrazolopyrimidine derivatives.

SUMMARY OF THE INVENTION

What we therefore believe to be comprised by our invention may be summarized inter alia in the following words:

A compound selected from those of Formula I

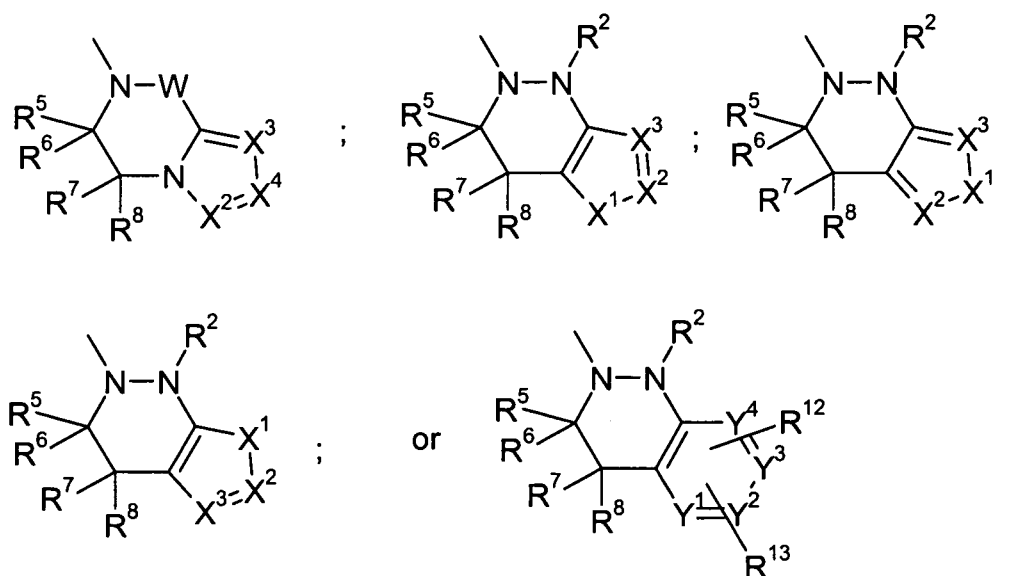


I

wherein

R¹ represents chloro or bromo;

A represents



wherein

W represents NR² or CR³R⁴, wherein

R² represents hydrogen, C₁₋₆alkyl, trifluoromethyl or cycloC₃₋₁₂alkyl;

R^3 , R^4 , R^5 , R^6 , which may be the same or different, each independently represent hydrogen, C_{1-6} alkyl, cyclo C_{3-12} alkyl, or trifluoromethyl;

R^7 , and R^8 , which may be the same or different, each independently represent hydrogen, C_{1-6} alkyl, cyclo C_{3-12} alkyl, amino, hydroxy, halogen, or trifluoromethyl;

X^1 represents CR^9R^{10} , NR^{11} , S, or O; and X^2 , X^3 , and X^4 , which may be the same or different each independently represent CR^9 or N, wherein

R^9 and R^{10} , which may be the same or different, each independently represent hydrogen, halogen, amino, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, aryl, C_{1-6} alkyl, cyclo C_{3-12} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, cyclo C_{3-12} alkyloxy, C_{2-6} alkenyloxy, C_{2-6} alkynyloxy, heteroaryl, heterocyclyl, aryloxy, heteroaryloxy, heterocyclyloxy, C_{1-6} alkylamino, di- C_{1-6} alkylamino, cyclo C_{3-12} alkylamino, di-cyclo C_{3-12} alkylamino, N- C_{1-6} alkyl-N-cyclo C_{3-12} alkylamino, C_{2-6} alkenylamino, C_{2-6} alkynylamino, di- C_{2-6} alkenylamino, di- C_{2-6} alkynylamino, N- C_{1-6} alkyl-N- C_{2-6} alkenylamino, N- C_{1-6} alkyl-N- C_{2-6} alkynylamino, N- C_{2-6} alkenyl-N-cyclo C_{3-12} alkylamino, N- C_{2-6} alkynyl-N-cyclo C_{3-12} alkylamino, N- C_{2-6} alkenyl-N- C_{2-6} alkynylamino, arylamino, diarylamino, aryl- C_{1-6} alkylamino, aryl- C_{2-6} alkenylamino, aryl- C_{2-6} alkynylamino, N-aryl-N-cyclo C_{3-12} alkylamino, heteroarylamino, diheteroarylamino, heteroaryl- C_{1-6} alkylamino, heteroaryl- C_{2-6} alkenylamino, heteroaryl- C_{2-6} alkynylamino, N-heteroaryl-N-cyclo C_{3-12} alkylamino, N-heteroaryl-N-arylamino, heterocyclylamino, diheterocyclylamino, heterocyclyl- C_{1-6} alkylamino, heterocyclyl- C_{2-6} alkenylamino, heterocyclyl- C_{2-6} alkynylamino, N-heterocyclyl-N-cyclo C_{3-12} alkylamino, N-heterocyclyl-N-arylamino, N-heterocyclyl-N-heteroarylamino, acyl, acyloxy, acylamino, C_{1-6} alkoxycarbonyl, cyclo C_{3-12} alkoxycarbonyl, C_{2-6} alkenyloxy carbonyl, C_{2-6}

alkynyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, heterocyclyloxycarbonyl, aminocarbonyl, C₁₋₆alkylaminocarbonyl, di-C₁₋₆alkylaminocarbonyl, cycloC₃₋₁₂alkylaminocarbonyl, di-cycloC₃₋₁₂alkylaminocarbonyl, N-C₁₋₆alkyl-N-cycloC₃₋₁₂alkylaminocarbonyl, C₂₋₆alkenylaminocarbonyl, C₂₋₆alkynylaminocarbonyl, di-C₂₋₆alkenylaminocarbonyl, di-C₂₋₆alkynylaminocarbonyl, N-C₁₋₆alkyl-N-C₂₋₆alkenylaminocarbonyl, N-C₁₋₆alkyl-N-C₂₋₆alkynylaminocarbonyl, N-C₂₋₆alkenyl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-C₂₋₆alkynyl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-C₂₋₆alkenyl-N-C₂₋₆alkynylaminocarbonyl, arylaminocarbonyl, diarylamino carbonyl, aryl-C₁₋₆alkylaminocarbonyl, aryl-C₂₋₆alkenylaminocarbonyl, aryl-C₂₋₆alkynylaminocarbonyl, N-aryl-N-cyclo C₃₋₇alkylaminocarbonyl, heteroarylaminocarbonyl, diheteroarylaminocarbonyl, heteroaryl-C₁₋₆alkylaminocarbonyl, heteroaryl-C₂₋₆alkenylaminocarbonyl, heteroaryl-C₂₋₆alkynylaminocarbonyl, N-heteroaryl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-heteroaryl-N-arylaminocarbonyl, heterocyclylaminocarbonyl, diheterocyclylaminocarbonyl, heterocyclyl-C₁₋₆alkylaminocarbonyl, heterocyclyl-C₂₋₆alkenylaminocarbonyl, heterocyclyl-C₂₋₆alkynylaminocarbonyl, N-heterocyclyl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-heterocyclyl-N-arylaminocarbonyl, N-heterocyclyl-Nheteroarylaminocarbonyl, C₁₋₆alkylsulfonyl, cycloC₃₋₁₂alkylsulfonyl, C₂₋₆alkenylsulfonyl, C₂₋₆alkynylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heterocyclylsulfonyl, C₁₋₆alkylsulfonyl, cycloC₃₋₁₂alkylsulfonyl, C₂₋₆alkenylsulfonyl, C₂₋₆alkynylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heterocyclylsulfonyl, C₁₋₆alkylsulfonylamino, or arylsulfonylamino and

R¹¹ represents hydrogen, C₁₋₆alkyl, cycloC₃₋₁₂alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, acyl, aryl, heteroaryl, heterocyclyl, C₁₋₆alkylaminocarbonyl, di-C₁₋₆alkylaminocarbonyl, C₁₋₆alkylsulfonyl, arylsulfonyl or heteroarylsulfonyl;

Y^1 , Y^2 , Y^3 , and Y^4 represent C or N, wherein at least two of Y^1 , Y^2 , Y^3 , and Y^4 represent C

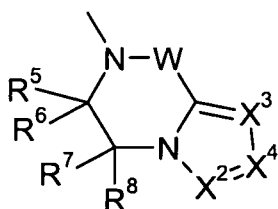
R^{12} and R^{13} , which may be the same or different, each independently represent hydrogen, halogen, amino, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, aryl, C_{1-6} alkyl, cyclo C_{3-12} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, cyclo C_{3-12} alkyloxy, C_{2-6} alkenyloxy, C_{2-6} alkynyloxy, heteroaryl, heterocyclyl, aryloxy, heteroaryloxy, heterocyclyloxy, C_{1-6} alkylamino, di- C_{1-6} alkylamino, cyclo C_{3-12} alkylamino, di-cyclo C_{3-12} alkylamino, N- C_{1-6} alkyl-N-cyclo C_{3-12} alkylamino, C_{2-6} alkenylamino, C_{2-6} alkynylamino, di- C_{2-6} alkenylamino, di- C_{2-6} alkynylamino, N- C_{1-6} alkyl-N- C_{2-6} alkenylamino, N- C_{1-6} alkyl-N- C_{2-6} alkynylamino, N- C_{2-6} alkenyl-N-cyclo C_{3-12} alkylamino, N- C_{2-6} alkynyl-N-cyclo C_{3-12} alkylamino, N- C_{2-6} alkenyl-N- C_{2-6} alkynylamino arylamino, diarylamino, aryl- C_{1-6} alkylamino, aryl- C_{2-6} alkenylamino, aryl- C_{2-6} alkynylamino, N-aryl-N-cyclo C_{3-12} alkylamino, heteroarylamino, diheteroarylamino, heteroaryl- C_{1-6} alkylamino, heteroaryl- C_{2-6} alkenylamino, heteroaryl- C_{2-6} alkynylamino, N-heteroaryl-N-cyclo C_{3-12} alkylamino, N-heteroaryl-N-arylamino, heterocyclylamino, diheterocyclylamino, heterocyclyl- C_{1-6} alkylamino, heterocyclyl- C_{2-6} alkenylamino, heterocyclyl- C_{2-6} alkynylamino, N-heterocyclyl-N-cyclo C_{3-12} alkylamino, N-heterocyclyl-N-arylamino, N-heterocyclyl-N-heteroarylamino, acyl, acyloxy, acylamino, C_{1-6} alkoxycarbonyl, cyclo C_{3-12} alkoxycarbonyl, C_{2-6} alkenyloxycarbonyl, C_{2-6} alkynyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, heterocyclyloxycarbonyl, aminocarbonyl, C_{1-6} alkylaminocarbonyl, di- C_{1-6} alkylaminocarbonyl, cyclo C_{3-12} alkylaminocarbonyl, di-cyclo C_{3-12} alkylaminocarbonyl, N- C_{1-6} alkyl-N-cyclo C_{3-12} alkylaminocarbonyl, C_{2-6} alkenylaminocarbonyl, C_{2-6} alkynylaminocarbonyl, di- C_{2-6} alkenylaminocarbonyl, di- C_{2-6} alkynylaminocarbonyl, N- C_{1-6} alkyl-N- C_{2-6} alkenylaminocarbonyl, N- C_{1-6} alkyl-N- C_{2-6} alkynylaminocarbonyl, N- C_{2-6} alkenyl-N-cyclo C_{3-12} alkylaminocarbonyl, N- C_{2-6} alkynyl-N-cyclo C_{3-12} alkylaminocarbonyl, N- C_{2-6} alkenyl-N- C_{2-6} alkynylaminocarbonyl, arylaminocarbonyl, diarylamino, aryl- C_{1-6} alkylaminocarbonyl, aryl- C_{2-6} alkenylaminocarbonyl, aryl- C_{2-6} alkynylaminocarbonyl, N-aryl-N-cyclo C_{3-7} alkylaminocarbonyl, heteroarylamino, diheteroarylamino, heteroaryl- C_{1-6} alkylaminocarbonyl, heteroaryl- C_{2-6}

C_6 alkenylaminocarbonyl, heteroaryl- C_{2-6} alkynylaminocarbonyl, N-heteroaryl-N-cyclo C_{3-12} alkylaminocarbonyl, N-heteroaryl-N-arylaminocarbonyl, heterocyclylaminocarbonyl, diheterocyclylaminocarbonyl, heterocyclyl- C_{1-6} alkylaminocarbonyl, heterocyclyl- C_{2-6} alkenylaminocarbonyl, heterocyclyl- C_{2-6} alkynylaminocarbonyl, N-heterocyclyl-N-cyclo C_{3-12} alkylaminocarbonyl, N-heterocyclyl-N-arylaminocarbonyl, N-heterocyclyl-Nheteroarylaminocarbonyl, C_{1-6} alkylsulfinyl, cyclo C_{3-12} alkylsulfinyl, C_{2-6} alkenylsulfinyl, C_{2-6} alkynylsulfinyl, arylsulfinyl, heteroarylsulfinyl, heterocyclylsulfinyl, C_{1-6} alkylsulfonyl, cyclo C_{3-12} alkylsulfonyl, C_{2-6} alkenylsulfonyl, C_{2-6} alkynylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heterocyclylsulfonyl, C_{1-6} alkylsulfonylamino, or arylsulfonylamino;

or R^{12} and R^{13} together with the two carbon atoms carrying them represent an aryl group which may be optionally substituted by a group selected from halogen, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, C_{1-6} alkyl, and C_{1-6} alkoxy; a heteroaryl group having 5 or 6 ring members which may be optionally substituted by a group selected from halogen, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, C_{1-6} alkyl, and C_{1-6} alkoxy; or a heterocyclyl group having 5 or 6 ring members, which may be optionally substituted by a group selected from oxo, halogen, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, C_{1-6} alkyl, and C_{1-6} alkoxy;

and optical isomers, pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof.

Such a compound of Formula I, wherein A represents



wherein R^5 , R^6 , R^7 , and R^8 , which may be the same or different, each independently represent hydrogen or C_{1-6} alkyl, and X^2 , X^3 , and X^4 , which may be the same or different represent CR^9 or N.

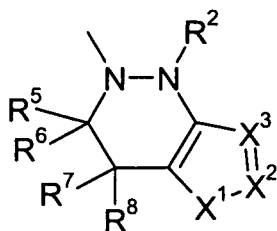
Such a compound of Formula I, wherein W represents CR^3R^4 , and R^3 and R^4 , which may be the same or different, each independently represent hydrogen or C_{1-6} alkyl, and R^9 represents hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylaminocarbonyl, cyclo C_{3-12} alkylaminocarbonyl, aryl or heteroaryl.

Such a compound of Formula I, wherein R^3 and R^4 , which may be the same or different, each independently represent hydrogen or methyl, and R^9 represents hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylaminocarbonyl, cyclo C_{3-12} alkylaminocarbonyl or a heteroaryl group selected from tetrazolyl, furyl, thienyl, pyridinyl, pyrimidinyl, and pyrazinyl, wherein the heteroaryl group may be optionally substituted by one or more groups selected from halogen and C_{1-6} alkyl.

Such a compound of Formula I, wherein W represents NR^2 , and R^2 represents hydrogen or C_{1-6} alkyl, and R^9 represents hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylaminocarbonyl, cyclo C_{3-12} alkylaminocarbonyl, aryl or heteroaryl.

Such a compound of Formula I, wherein R^2 represents hydrogen or methyl.

Such a compound of Formula I, wherein A represents

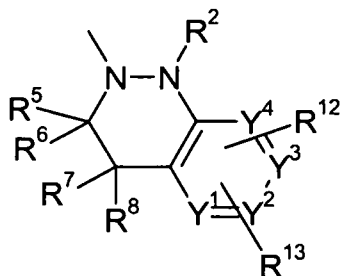


wherein R^2 , R^5 , R^6 , R^7 , and R^8 , which may be the same or different, each independently represent hydrogen or C_{1-6} alkyl.

Such a compound of Formula I, wherein X^1 represents NR^{11} , wherein R^{11} represents hydrogen or C_{1-6} alkyl, S, or O and X^2 and X^3 represent CR^9 .

Such a compound of Formula I, wherein R^9 represents hydrogen, halogen, or C_{1-6} alkyl.

Such a compound of Formula I, wherein A represents



wherein R^2 , R^5 , R^6 , R^7 , and R^8 , which may be the same or different, each independently represent hydrogen or C_{1-6} alkyl.

Such a compound of Formula I, wherein R^2 , R^5 , R^6 , R^7 , and R^8 , which may be the same or different, each independently represent hydrogen or methyl.

Such a compound of Formula I, wherein R^{12} and R^{13} , which may be the same or different, each independently represent hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylsulphonyl, trifluoromethyl, aryl, heteroaryl, or C_{1-6} alkylcarbonylamino.

Such a compound of Formula I, wherein one of R^{12} and R^{13} represents hydrogen and the other represents hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylsulphonyl, trifluoromethyl, aryl, heteroaryl, or C_{1-6} alkylcarbonylamino.

Specific compounds of Formula I within the present invention include, but are not limited to, the following compounds (or salts thereof):

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6-dimethyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6-dimethyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(4-methyl-6,7-dihydro-4H-[1,2,3]triazolo[1,5-a]pyrazin-5-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dihydro-4H-[1,2,3]triazolo[1,5-a]pyrazin-5-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(4-methyl-6,7-dihydro-4H-[1,2,3]triazolo[1,5-a]pyrazin-5-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dihydro-4H-[1,2,3]triazolo[1,5-a]pyrazin-5-yl)-methanone

7-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-8-methyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine-2-carboxylic acid ethyl ester

7-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine-2-carboxylic acid ethyl ester

7-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-8-methyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine-2-carboxylic acid ethyl ester

7-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine-2-carboxylic acid ethyl ester

7-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-8-methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine-3-carboxylic acid ethyl ester

7-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-5,6,7,8-tetrahydro-
[1,2,4]triazolo[4,3-a]pyrazine-3-carboxylic acid ethyl ester
7-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-8-methyl-5,6,7,8-tetrahydro-
[1,2,4]triazolo[4,3-a]pyrazine-3-carboxylic acid ethyl ester
7-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-5,6,7,8-tetrahydro-
[1,2,4]triazolo[4,3-a]pyrazine-3-carboxylic acid ethyl ester
(3-Bromo-8-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-(6-chloro-
pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
(3-Bromo-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-(6-chloro-
pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
(3-Bromo-8-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-(6-bromo-
pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
(3-Bromo-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-(6-bromo-
pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-5,6-dihydro-8H-
[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(5,6-dihydro-8H-[1,2,4]triazolo[4,3-
a]pyrazin-7-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-5,6-dihydro-8H-
[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5,6-dihydro-8H-[1,2,4]triazolo[4,3-
a]pyrazin-7-yl)-methanone
(6-Chloro-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-(6-chloro-
pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
(6-Chloro-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-(6-chloro-pyrazolo[1,5-
a]pyrimidin-2-yl)-methanone
(6-Chloro-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-(6-bromo-
pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
(6-Chloro-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-(6-bromo-pyrazolo[1,5-
a]pyrimidin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dibromo-1-methyl-3,4-dihydro-1H-
pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dibromo-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dibromo-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dibromo-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Bromo-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

(6-Bromo-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

(6-Bromo-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

(6-Bromo-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-5-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-5-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-5-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-5-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(2,8-dimethyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(2-methyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(2,8-dimethyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(2-methyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3,8-dimethyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-methyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3,8-dimethyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-methyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3,8-dimethyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3,8-dimethyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carbonitrile

2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carbonitrile

2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carbonitrile

2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carbonitrile

2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid methylamide

2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid methylamide

2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid methylamide

2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid methylamide

2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid cyclopropylamide

2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid cyclopropylamide

2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid cyclopropylamide

2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid cyclopropylamide

2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid ethylamide

2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid ethylamide

2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid ethylamide

2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid ethylamide

2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid isopropylamide

2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid isopropylamide

2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid isopropylamide

2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid isopropylamide

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-6-(1H-tetrazol-5-yl)-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[6-(1H-tetrazol-5-yl)-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-6-(1H-tetrazol-5-yl)-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[6-(1H-tetrazol-5-yl)-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyridin-2-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyridin-2-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyridin-2-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyridin-2-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyridin-3-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyridin-3-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyridin-3-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyridin-3-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyridin-4-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyridin-4-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyridin-4-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyridin-4-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-thiophen-2-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-thiophen-2-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-thiophen-2-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-thiophen-2-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-furan-2-yl-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-furan-2-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-furan-2-yl-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-furan-2-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-thiophen-3-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-thiophen-3-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-thiophen-3-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-thiophen-3-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-furan-3-yl-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-furan-3-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-furan-3-yl-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-furan-3-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyrimidin-4-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyrimidin-4-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyrimidin-4-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyrimidin-4-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyrimidin-5-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyrimidin-5-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyrimidin-5-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyrimidin-5-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-3-pyridin-2-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-pyridin-2-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-3-pyridin-2-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-pyridin-2-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-3-pyridin-3-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-pyridin-3-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-3-pyridin-3-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-pyridin-3-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-3-pyridin-4-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-pyridin-4-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-3-pyridin-4-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-pyridin-4-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-3-thiophen-2-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-thiophen-2-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-3-thiophen-2-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-thiophen-2-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-furan-2-yl-8-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-furan-2-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-furan-2-yl-8-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-furan-2-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-3-thiophen-3-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-thiophen-3-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-3-thiophen-3-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-thiophen-3-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-furan-3-yl-8-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-furan-3-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-furan-3-yl-8-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-furan-3-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-3-pyrimidin-4-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-pyrimidin-4-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-3-pyrimidin-4-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-pyrimidin-4-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-3-pyrimidin-5-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

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(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-3-pyrimidin-5-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-pyrimidin-5-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(6-fluoro-pyridin-3-yl)-8-methyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(6-fluoro-pyridin-3-yl)-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(6-fluoro-pyridin-3-yl)-8-methyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(6-fluoro-pyridin-3-yl)-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(2-fluoro-pyridin-3-yl)-8-methyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(2-fluoro-pyridin-3-yl)-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(2-fluoro-pyridin-3-yl)-8-methyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(2-fluoro-pyridin-3-yl)-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[2-(6-fluoro-pyridin-3-yl)-8-methyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[2-(6-fluoro-pyridin-3-yl)-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[2-(6-fluoro-pyridin-3-yl)-8-methyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[2-(6-fluoro-pyridin-3-yl)-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[2-(2-fluoro-pyridin-3-yl)-8-methyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[2-(2-fluoro-pyridin-3-yl)-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[2-(2-fluoro-pyridin-3-yl)-8-methyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[2-(2-fluoro-pyridin-3-yl)-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(6-fluoro-pyridin-3-yl)-8-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(6-fluoro-pyridin-3-yl)-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(6-fluoro-pyridin-3-yl)-8-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(6-fluoro-pyridin-3-yl)-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(2-fluoro-pyridin-3-yl)-8-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(2-fluoro-pyridin-3-yl)-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(2-fluoro-pyridin-3-yl)-8-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(2-fluoro-pyridin-3-yl)-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-thieno[3,2-c]pyridazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-thieno[3,2-c]pyridazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6-dimethyl-3,4-dihydro-1H-thieno[3,2-c]pyridazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6-dimethyl-3,4-dihydro-1H-thieno[3,2-c]pyridazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,7-dimethyl-3,4-dihydro-1H-thieno[3,2-c]pyridazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,7-dimethyl-3,4-dihydro-1H-thieno[3,2-c]pyridazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6,7-trimethyl-3,4-dihydro-1H-thieno[3,2-c]pyridazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6,7-trimethyl-3,4-dihydro-1H-thieno[3,2-c]pyridazin-2-yl)-methanone

(6-Bromo-1-methyl-3,4-dihydro-1H-thieno[3,2-c]pyridazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

(6-Bromo-1-methyl-3,4-dihydro-1H-thieno[3,2-c]pyridazin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

(6-Chloro-1-methyl-3,4-dihydro-1H-thieno[3,2-c]pyridazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

(6-Bromo-1-methyl-3,4-dihydro-1H-thieno[3,2-c]pyridazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-furo[3,2-c]pyridazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-furo[3,2-c]pyridazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6-dimethyl-3,4-dihydro-1H-furo[3,2-c]pyridazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6-dimethyl-3,4-dihydro-1H-furo[3,2-c]pyridazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,7-dimethyl-3,4-dihydro-1H-furo[3,2-c]pyridazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,7-dimethyl-3,4-dihydro-1H-furo[3,2-c]pyridazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6,7-trimethyl-3,4-dihydro-1H-furo[3,2-c]pyridazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6,7-trimethyl-3,4-dihydro-1H-furo[3,2-c]pyridazin-2-yl)-methanone

(6-Bromo-1-methyl-3,4-dihydro-1H-furo[3,2-c]pyridazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

(6-Bromo-1-methyl-3,4-dihydro-1H-furo[3,2-c]pyridazin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

(6-Chloro-1-methyl-3,4-dihydro-1H-furo[3,2-c]pyridazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

(6-Bromo-1-methyl-3,4-dihydro-1H-furo[3,2-c]pyridazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-1,3,4,5-tetrahydro-pyrrolo[3,2-c]pyridazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-1,3,4,5-tetrahydro-pyrrolo[3,2-c]pyridazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6-dimethyl-1,3,4,5-tetrahydro-pyrrolo[3,2-c]pyridazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6-dimethyl-1,3,4,5-tetrahydro-pyrrolo[3,2-c]pyridazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,7-dimethyl-1,3,4,5-tetrahydro-pyrrolo[3,2-c]pyridazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,7-dimethyl-1,3,4,5-tetrahydro-pyrrolo[3,2-c]pyridazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6,7-trimethyl-1,3,4,5-tetrahydro-pyrrolo[3,2-c]pyridazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6,7-trimethyl-1,3,4,5-tetrahydro-pyrrolo[3,2-c]pyridazin-2-yl)-methanone

(6-Bromo-1-methyl-1,3,4,5-tetrahydro-pyrrolo[3,2-c]pyridazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

(6-Bromo-1-methyl-1,3,4,5-tetrahydro-pyrrolo[3,2-c]pyridazin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

(6-Chloro-1-methyl-1,3,4,5-tetrahydro-pyrrolo[3,2-c]pyridazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

(6-Bromo-1-methyl-1,3,4,5-tetrahydro-pyrrolo[3,2-c]pyridazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

(8-Chloro-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

(8-Bromo-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

(7-Chloro-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

(7-Bromo-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

(6-Chloro-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

(6-Bromo-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

(5-Chloro-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

(5-Bromo-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
(8-Bromo-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
(8-Bromo-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
(7-Bromo-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
(7-Bromo-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
(6-Bromo-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
(6-Bromo-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
(5-Bromo-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
(5-Bromo-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
(8-Fluoro-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
(8-Fluoro-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
(7-Fluoro-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
(7-Fluoro-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
(6-Fluoro-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
(6-Fluoro-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
(5-Fluoro-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

(5-Fluoro-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,8-dimethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,8-dimethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,7-dimethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,7-dimethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6-dimethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6-dimethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,5-dimethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,5-dimethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methoxy-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methoxy-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-methoxy-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-methoxy-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-methoxy-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-methoxy-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-methoxy-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-methoxy-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-8-trifluoromethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-8-trifluoromethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-trifluoromethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-trifluoromethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-trifluoromethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-trifluoromethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-5-trifluoromethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-5-trifluoromethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

N-[2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-cinnolin-8-yl]-acetamide

N-[2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-cinnolin-8-yl]-acetamide

N-[2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-cinnolin-7-yl]-acetamide

N-[2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-cinnolin-7-yl]-acetamide

N-[2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-cinnolin-6-yl]-acetamide

N-[2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-cinnolin-6-yl]-acetamide

N-[2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-cinnolin-5-yl]-acetamide

N-[2-(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-cinnolin-5-yl]-acetamide

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methanesulfonyl-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methanesulfonyl-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-methanesulfonyl-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-methanesulfonyl-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-methanesulfonyl-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-methanesulfonyl-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-methanesulfonyl-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-methanesulfonyl-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-pyrido[2,3-c]pyridazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-pyrido[2,3-c]pyridazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-pyrido[3,4-c]pyridazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-pyrido[3,4-c]pyridazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-pyrido[4,3-c]pyridazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-pyrido[4,3-c]pyridazin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-pyrido[3,2-c]pyridazin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-pyrido[3,2-c]pyridazin-2-yl)-methanone

(7-Bromo-1-methyl-3,4-dihydro-1H-pyrido[3,2-c]pyridazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

(7-Bromo-1-methyl-3,4-dihydro-1H-pyrido[3,2-c]pyridazin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-8-pyridin-4-yl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-8-pyridin-4-yl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-pyridin-4-yl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-pyridin-4-yl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyridin-4-yl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyridin-4-yl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-5-pyridin-4-yl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-5-pyridin-4-yl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[8-(2-fluoro-pyridin-4-yl)-1-methyl-3,4-dihydro-1H-cinnolin-2-yl]-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[8-(2-fluoro-pyridin-4-yl)-1-methyl-3,4-dihydro-1H-cinnolin-2-yl]-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[7-(2-fluoro-pyridin-4-yl)-1-methyl-3,4-dihydro-1H-cinnolin-2-yl]-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[7-(2-fluoro-pyridin-4-yl)-1-methyl-3,4-dihydro-1H-cinnolin-2-yl]-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[6-(2-fluoro-pyridin-4-yl)-1-methyl-3,4-dihydro-1H-cinnolin-2-yl]-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[6-(2-fluoro-pyridin-4-yl)-1-methyl-3,4-dihydro-1H-cinnolin-2-yl]-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[5-(2-fluoro-pyridin-4-yl)-1-methyl-3,4-dihydro-1H-cinnolin-2-yl]-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[5-(2-fluoro-pyridin-4-yl)-1-methyl-3,4-dihydro-1H-cinnolin-2-yl]-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-7-(2H-tetrazol-5-yl)-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-methanone

The invention also relates to compounds of the Formula I which are marked by radioactive atoms. Typical compounds include those where one or more hydrogens are substituted by tritium, where one or more C¹² are substituted by C¹⁴, where one or more fluor atoms are substituted by F¹⁸ or other isotopes. These can be used for the treatment of diseases (e.g. cancer) but also for diagnostic purposes. The radioactive atoms exchanged in the molecule are often isotopes of carbon, hydrogen, halogen, sulphur or phosphorus.

The invention in general relates to the use of a metabotropic glutamate receptor modulator (and in particular of a mGluR5 modulator) for the preparation of a medicament and for the treatment of various diseases as mentioned hereunder in a mammal, including humans.

Moreover, the invention relates to the use of a compound of Formula I as defined above or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof for the preparation of a medicament and for the treatment of a mammal, including humans.

Further, the invention relates to the use of a compound for the preparation of a medicament for treating or preventing a condition or disease associated with abnormal glutamate neurotransmission. Such a use includes the use of a compound for the preparation of a medicament for the prevention and/or treatment of a condition or disease in an animal including a human being which condition or

disease is affected or facilitated by the negative modulatory effect of mGluR5 modulators.

The invention is dealing with the use of a mGluR5 modulator and in particular a compound according to Formula I, for the preparation of a medicament, including for the conditions or diseases selected from those mentioned earlier in the description.

The invention also relates to the use of a mGluR5 modulator, in particular a compound according to Formula I wherein the condition associated with abnormal glutamate neurotransmission is selected from those mentioned earlier in the description.

Further, the invention relates to the use of a compound wherein the condition associated with abnormal glutamate neurotransmission is selected from: neuropathic pain, diabetic neuropathic pain (DNP), cancer pain, pain related to rheumatic arthritis, inflammatory pain, L-dopa-induced and tardive dyskinesias, Parkinson's disease, anxiety disorders, Huntington's chorea, epilepsy, Alzheimer's disease, positive and negative symptoms of schizophrenia, cognitive impairment, reflux, migraine or for cognitive enhancement and/or neuroprotection.

Moreover, the invention relates to a method for treating or preventing a condition or disease associated with abnormal glutamate neurotransmission, including a condition or disease which is affected or facilitated by modulation of the mGluR5 receptor, including for the conditions or diseases selected from those described earlier in the description, such method comprising the step of administering a therapeutically effective amount of a compound selected from those of Formula I as defined above to a subject in need thereof.

Further, the invention relates to a pharmaceutical composition comprising as active ingredient at least one compound of Formula I as defined above or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof, together with one or more pharmaceutically acceptable excipients.

Moreover, the mGluR modulators as described above are expected to have a high activity when administered in combination with other substances exhibiting neurological effects via different mechanisms.

The invention also relates to a pharmaceutical composition comprising at least two different active ingredients, containing at least one compound of Formula I as defined above, and furthermore containing at least one NMDA-antagonist, together with one or more pharmaceutically acceptable excipients. These compositions can be used for the treatment of CNS-related diseases, cognitive enhancement and for neuro-protection.

Simultaneous administration of Group I mGluR modulators and NMDA receptor antagonists has also been shown to provide neuroprotection in animal models (see e.g. Zieminska et al. *Neurochemistry International*, 2006, 66, 301-309; Zieminska et al. *Neurochemistry International*, 2003, 43, 481-492; Zieminska et al. *Neurochemistry International*, 2006, 48, 491-497).

With respect to the specific compounds as described above, the combined therapy exhibits a greater neuroprotective effect than monotherapy with either an mGluR modulator or an NMDA receptor antagonist. As particularly active NMDA receptor antagonist, the compound Memantine can be named, which is also known as 1-amino-3,5-dimethyladamantane (see US 4,122,193; US 4,273,774; and US 5,061,703).

Furthermore, the compound Neramexane, which also is known as 1-amino-1,3,3,5,5-pentamethylcyclohexane, is a further active NMDA receptor antagonist and is disclosed in detail in US 6,034,134 and US 6,071,966. Memantine and Neramexane are systemically-active noncompetitive NMDA receptor antagonists having moderate affinity for the receptor. They exhibit strong voltage dependent characteristics and fast blocking/unblocking kinetics (see e.g. Görtelmeyer et al., *Arzneim-Forsch/Drug Res.*, 1992, 42:904-913; Winblad et al., *Int. J. Geriatr. Psychiatry*, 1999, 14:135-146; Rogawski, *Amino Acids*, 2000, 19: 133-49; Danysz

et al., Curr. Pharm. Des., 2002, 8:835-43; Jirgensons et. al. Eur. J. Med. Chem., 2000, 35: 555-565).

The combination of NMDA antagonists with mGluR5 modulators can be realized in a single pharmaceutical composition (as principally described in the prior art) comprising a mGluR5 modulator of the present invention and an NMDA receptor antagonist, in one pharmaceutical formulation, or in two separate pharmaceutical compositions or formulations, one comprising a mGluR5 modulator of the present invention and one comprising an NMDA receptor antagonist in a pharmaceutical formulation, to be administered conjointly (simultaneously or sequentially). For the sequential administration to be considered "conjoint", however, the mGluR5 modulator of the present invention and the NMDA receptor antagonist must be administered separated by a time interval that still permits the resultant beneficial effect in a mammal. For example, the mGluR5 modulator of the present invention and the NMDA receptor antagonist must be administered on the same day (e.g., each - once or twice daily), preferably within an hour of each other, and most preferably simultaneously.

This invention also relates to a pharmaceutical composition comprising a combination of a compound of Formula I as described above and an NMDA receptor antagonist. Of particular interest is a composition, wherein the NMDA receptor antagonist is selected from Memantine and Neramexane (or a combination thereof) and pharmaceutically acceptable salts, polymorphs, hydrates and solvates thereof.

The invention also relates to a pharmaceutical composition comprising at least two different active ingredients, containing at least one compound of Formula I as defined above, and furthermore containing at least one of L-DOPA, another dopaminomimetics (in particular an antiparkinsonian dopaminomimetics e.g. bromocriptine, cabergolin, ropinirole, pramiperole, pergolide, rotigotine), and a neuroleptic (in particular a classical neuroleptic, e.g. haloperidol, perphenazin, chlorpromazine, metoclopramide).

These combination products can e.g. be used for the treatment of CNS-related disorders and diseases. Because of the antidyskinetic effect of the compounds of Formula I, drug induced dyskinesias, neuroleptic-induced dyskinesias, haloperidol-induced dyskinesias, dopaminomimetic-induced dyskinesias can be treated in addition to the conditions which are typically treated with L-Dopa, dopaminomimetics or neuroleptics.

The invention also relates to a method of providing neuroprotection to a living animal, including a human, comprising the step of administering to a living animal, including a human, a therapeutically effective amount of a composition as described above.

This invention is also dealing with the compounds of Formula I for the use as a medicament. Furthermore, the invention relates to the use of a compound of Formula I for the manufacture of a medicament for the treatment of the diseases and conditions mentioned above.

Furthermore, the invention relates to the use of a composition as described above for the manufacture of a medicament to provide neuroprotection in an animal, including a human.

Furthermore, the invention relates to the use of a compound of Formula I in the manufacture of a medicament for treatment of a condition associated with abnormal glutamate neurotransmission or in which modulation of mGluR5 receptors results in therapeutic benefit. The disorders which can be treated have already been described above. Such conditions and indications include:

a) For mGluR5 modulators: chronic pain, neuropathic pain, diabetic neuropathic pain (DNP), cancer pain, pain related to rheumatic arthritis, inflammatory pain, L-dopa-induced dyskinesias, dopaminomimetic-induced dyskinesias, L-dopa-induced dyskinesias in Parkinson's disease therapy, dopaminomimetic-induced dyskinesias in Parkinson's disease therapy, tardive dyskinesias, Parkinson's disease, anxiety disorders, panic disorders, anxiety and panic disorders, social anxiety disorder

(SAD), generalized anxiety disorder, substance-induced anxiety disorder, eating disorders, obesity, binge eating disorders, Huntington's chorea, epilepsy, Alzheimer's disease, positive and negative symptoms of schizophrenia, cognitive impairment, functional gastrointestinal disorders, gastroesophageal reflux disease (GERD), migraine, irritable bowel syndrome (IBS), or for cognitive enhancement and/or neuroprotection.

b) For negative modulation of mGluR5: chronic pain, neuropathic pain, diabetic neuropathic pain (DNP), cancer pain, pain related to rheumatic arthritis, inflammatory pain, L-dopa-induced dyskinesias, dopaminomimetic-induced dyskinesias, L-dopa-induced dyskinesias in Parkinson's disease therapy, dopaminomimetic-induced dyskinesias in Parkinson's disease therapy, tardive dyskinesias, Parkinson's disease, anxiety disorders, panic disorders, anxiety and panic disorders, social anxiety disorder (SAD), generalized anxiety disorder, substance-induced anxiety disorder, eating disorders, obesity, binge eating disorders, migraine, irritable bowel syndrome (IBS), functional gastrointestinal disorders, gastroesophageal reflux disease (GERD), Huntington's chorea and/or epilepsy.

c) For positive modulation of mGluR5: Alzheimer's disease, positive and/or negative symptoms of schizophrenia, cognitive impairment, or for cognitive enhancement and/or neuroprotection.

The mGluR5 negative modulators in general and in particular the compounds of Formula I according to the invention can be used for the treatment of binge eating disorders.

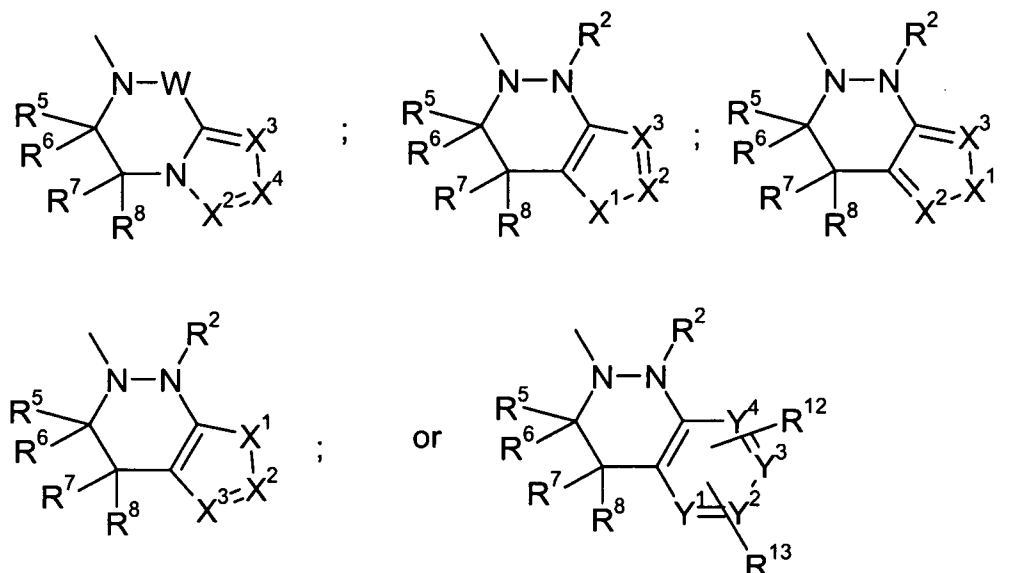
The invention also relates to the process for the synthesis or preparation of a compound of Formula I



wherein

R^1 represents chloro or bromo;

A represents



wherein

W represents NR^2 or CR^3R^4

R^2 represents hydrogen, C_{1-6} alkyl, trifluoromethyl or cyclo C_{3-12} alkyl;

R^3 , R^4 , R^5 , R^6 , which may be the same or different, each independently represent hydrogen, C_{1-6} alkyl, cyclo C_{3-12} alkyl, or trifluoromethyl;

R^7 , and R^8 , which may be the same or different, each independently represent hydrogen, C_{1-6} alkyl, cyclo C_{3-12} alkyl, amino, hydroxy, halogen, or trifluoromethyl;

X^1 represents CR^9R^{10} , NR^{11} , S, or O, and X^2 , X^3 , and X^4 , which may be the same or different each independently represent CR^9 or N, wherein

R^9 and R^{10} , which may be the same or different, each independently represent hydrogen, halogen, amino, hydroxy, nitro, cyano,

trifluoromethyl, trifluoromethoxy, aryl, C₁₋₆alkyl, cycloC₃₋₁₂alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, cycloC₃₋₁₂alkyloxy, C₂₋₆alkenyloxy, C₂₋₆alkynyloxy, heteroaryl, heterocyclyl, aryloxy, heteroaryloxy, heterocyclyloxy, C₁₋₆alkylamino, di-C₁₋₆alkylamino, cycloC₃₋₁₂alkylamino, di-cycloC₃₋₁₂alkylamino, N-C₁₋₆alkyl-N-cycloC₃₋₁₂alkylamino, C₂₋₆alkenylamino, C₂₋₆alkynylamino, di-C₂₋₆alkenylamino, di-C₂₋₆alkynylamino, N-C₁₋₆alkyl-N-C₂₋₆alkenylamino, N-C₁₋₆alkyl-N-C₂₋₆alkynylamino, N-C₂₋₆alkenyl-N-cycloC₃₋₁₂alkylamino, N-C₂₋₆alkynyl-N-cycloC₃₋₁₂alkylamino, N-C₂₋₆alkenyl-N-C₂₋₆alkynylamino, arylamino, diarylamino, aryl-C₁₋₆alkylamino, aryl-C₂₋₆alkenylamino, aryl-C₂₋₆alkynylamino, N-aryl-N-cycloC₃₋₁₂alkylamino, heteroarylamino, diheteroarylamino, heteroaryl-C₁₋₆alkylamino, heteroaryl-C₂₋₆alkenylamino, heteroaryl-C₂₋₆alkynylamino, N-heteroaryl-N-cycloC₃₋₁₂alkylamino, N-heteroaryl-N-arylamino, heterocyclylamino, diheterocyclylamino, heterocyclyl-C₁₋₆alkylamino, heterocyclyl-C₂₋₆alkenylamino, heterocyclyl-C₂₋₆alkynylamino, N-heterocyclyl-N-cycloC₃₋₁₂alkylamino, N-heterocyclyl-N-arylamino, N-heterocyclyl-N-heteroarylamino, acyl, acyloxy, acylamino, C₁₋₆alkoxycarbonyl, cycloC₃₋₁₂alkoxycarbonyl, C₂₋₆alkenyloxy carbonyl, C₂₋₆alkynyloxy carbonyl, aryloxy carbonyl, heteroaryloxy carbonyl, heterocyclyloxy carbonyl, aminocarbonyl, C₁₋₆alkylaminocarbonyl, di-C₁₋₆alkylaminocarbonyl, cycloC₃₋₁₂alkylaminocarbonyl, di-cycloC₃₋₁₂alkylaminocarbonyl, N-C₁₋₆alkyl-N-cycloC₃₋₁₂alkylaminocarbonyl, C₂₋₆alkenylaminocarbonyl, C₂₋₆alkynylaminocarbonyl, di-C₂₋₆alkenylaminocarbonyl, di-C₂₋₆alkynylaminocarbonyl, N-C₁₋₆alkyl-N-C₂₋₆alkenylaminocarbonyl, N-C₁₋₆alkyl-N-C₂₋₆alkynylaminocarbonyl, N-C₂₋₆alkenyl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-C₂₋₆alkynyl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-C₂₋₆alkenyl-N-C₂₋₆alkynylaminocarbonyl, arylaminocarbonyl, diarylamino carbonyl, aryl-C₁₋₆alkylaminocarbonyl, aryl-C₂₋₆alkenylaminocarbonyl, aryl-C₂₋₆alkynylaminocarbonyl, N-aryl-N-cyclo C₃₋₇alkylaminocarbonyl,

heteroarylaminocarbonyl, diheteroarylaminocarbonyl, heteroaryl-C₁₋₆alkylaminocarbonyl, heteroaryl-C₂₋₆alkenylaminocarbonyl, heteroaryl-C₂₋₆alkynylaminocarbonyl, N-heteroaryl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-heteroaryl-N-arylaminocarbonyl, heterocyclylaminocarbonyl, diheterocyclylaminocarbonyl, heterocyclyl-C₁₋₆alkylaminocarbonyl, heterocyclyl-C₂₋₆alkenylaminocarbonyl, heterocyclyl-C₂₋₆alkynylaminocarbonyl, N-heterocyclyl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-heterocyclyl-N-arylaminocarbonyl, N-heterocyclyl-Nheteroarylaminocarbonyl, C₁₋₆alkylsulfinyl, cycloC₃₋₁₂alkylsulfinyl, C₂₋₆alkenylsulfinyl, C₂₋₆alkynylsulfinyl, arylsulfinyl, heteroarylsulfinyl, heterocyclylsulfinyl, C₁₋₆alkylsulfonyl, cycloC₃₋₁₂alkylsulfonyl, C₂₋₆alkenylsulfonyl, C₂₋₆alkynylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heterocyclylsulfonyl, C₁₋₆alkylsulfonylamino, or arylsulfonylamino and

R¹¹ represents hydrogen, C₁₋₆alkyl, cycloC₃₋₁₂alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, acyl, aryl, heteroaryl, heterocyclyl, C₁₋₆alkylaminocarbonyl, di-C₁₋₆alkylaminocarbonyl, C₁₋₆alkylsulfonyl, arylsulfonyl or heteroarylsulfonyl;

Y¹, Y², Y³, and Y⁴ represent C or N, wherein at least two of Y¹, Y², Y³, and Y⁴ represent C;

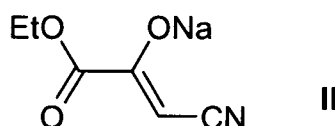
R¹² and R¹³, which may be the same or different, each independently represent hydrogen, halogen, amino, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, aryl, C₁₋₆alkyl, cycloC₃₋₁₂alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, cycloC₃₋₁₂alkyloxy, C₂₋₆alkenyloxy, C₂₋₆alkynyloxy, heteroaryl, heterocyclyl, aryloxy, heteroaryloxy, heterocycliloxy, C₁₋₆alkylamino, di-C₁₋₆alkylamino, cycloC₃₋₁₂alkylamino, di-cycloC₃₋₁₂alkylamino, N-C₁₋₆alkyl-N-cycloC₃₋₁₂alkylamino, C₂₋₆alkenylamino, C₂₋₆alkynylamino, di-C₂₋₆alkenylamino, di-C₂₋₆alkynylamino, N-C₁₋₆alkyl-N-C₂₋₆alkenylamino, N-C₁₋₆alkyl-N-C₂₋₆alkynylamino, N-C₂₋₆alkenyl-N-cycloC₃₋₁₂alkylamino, N-C₂₋₆alkynyl-N-cycloC₃₋₁₂alkylamino, N-C₂₋₆alkenyl-N-C₂₋

alkynylamino arylamino, diarylamino, aryl-C₁₋₆alkylamino, aryl-C₂₋₆alkenylamino, aryl-C₂₋₆alkynylamino, N-aryl-N-cycloC₃₋₁₂alkylamino, heteroarylamino, diheteroarylamino, heteroaryl-C₁₋₆alkylamino, heteroaryl-C₂₋₆alkenylamino, heteroaryl-C₂₋₆alkynylamino, N-heteroaryl-N-cycloC₃₋₁₂alkylamino, N-heteroaryl-N-arylamino, heterocyclylamino, diheterocyclylamino, heterocyclyl-C₁₋₆alkylamino, heterocyclyl-C₂₋₆alkenylamino, heterocyclyl-C₂₋₆alkynylamino, N-heterocyclyl-N-cycloC₃₋₁₂alkylamino, N-heterocyclyl-N-arylamino, N-heterocyclyl-N-heteroarylamino, acyl, acyloxy, acylamino, C₁₋₆alkoxycarbonyl, cycloC₃₋₁₂alkoxycarbonyl, C₂₋₆alkenyloxycarbonyl, C₂₋₆alkynyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, heterocyclilyloxycarbonyl, aminocarbonyl, C₁₋₆alkylaminocarbonyl, di-C₁₋₆alkylaminocarbonyl, cycloC₃₋₁₂alkylaminocarbonyl, di-cycloC₃₋₁₂alkylaminocarbonyl, N-C₁₋₆alkyl-N-cycloC₃₋₁₂alkylaminocarbonyl, C₂₋₆alkenylaminocarbonyl, C₂₋₆alkynylaminocarbonyl, di-C₂₋₆alkenylaminocarbonyl, di-C₂₋₆alkynylaminocarbonyl, N-C₁₋₆alkyl-N-C₂₋₆alkenylaminocarbonyl, N-C₁₋₆alkyl-N-C₂₋₆alkynylaminocarbonyl, N-C₂₋₆alkenyl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-C₂₋₆alkynyl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-C₂₋₆alkenyl-N-C₂₋₆alkynylaminocarbonyl, arylaminocarbonyl, diarylamino, aryl-C₁₋₆alkylaminocarbonyl, aryl-C₂₋₆alkenylaminocarbonyl, aryl-C₂₋₆alkynylaminocarbonyl, N-aryl-N-cyclo C₃₋₇alkylaminocarbonyl, heteroarylaminocarbonyl, diheteroarylaminocarbonyl, heteroaryl-C₁₋₆alkylaminocarbonyl, heteroaryl-C₂₋₆alkenylaminocarbonyl, heteroaryl-C₂₋₆alkynylaminocarbonyl, N-heteroaryl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-heteroaryl-N-arylaminocarbonyl, heterocyclylaminocarbonyl, diheterocyclylaminocarbonyl, heterocyclyl-C₁₋₆alkylaminocarbonyl, heterocyclyl-C₂₋₆alkenylaminocarbonyl, heterocyclyl-C₂₋₆alkynylaminocarbonyl, N-heterocyclyl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-heterocyclyl-N-arylaminocarbonyl, N-heterocyclyl-Nheteroarylaminocarbonyl, C₁₋₆alkylsulfinyl, cycloC₃₋₁₂alkylsulfinyl, C₂₋₆alkenylsulfinyl, C₂₋₆alkynylsulfinyl, arylsulfinyl, heteroarylsulfinyl, heterocyclylsulfinyl, C₁₋₆alkylsulfonyl, cycloC₃₋₁₂alkylsulfonyl, C₂₋₆alkenylsulfonyl, C₂₋₆alkynylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heterocyclylsulfonyl, C₁₋₆alkylsulfonylamino, or arylsulfonylamino;

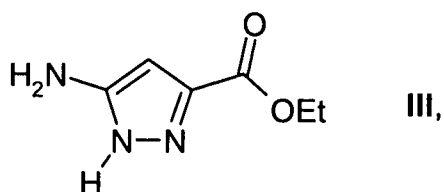
or R¹² and R¹³ together with the two carbon atoms carrying them represent an aryl group which may be optionally substituted by a group selected from halogen, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl, and C₁₋₆alkoxy; a heteroaryl group having 5 or 6 ring members which may be optionally substituted by a group selected from halogen, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl, and C₁₋₆alkoxy; or a heterocyclyl group having 5 or 6 ring members, which may be optionally substituted by a group selected from oxo, halogen, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl, and C₁₋₆alkoxy;

and optical isomers, pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof,

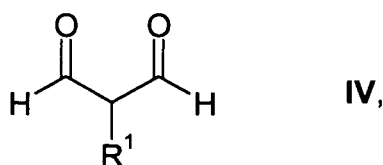
wherein a compound of Formula II



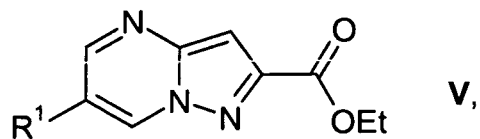
is suspended in a mixture of ethanol and water and treated with hydrochloric acid, followed by reaction with H₂NNHCOOCH₃ to yield a compound of Formula III



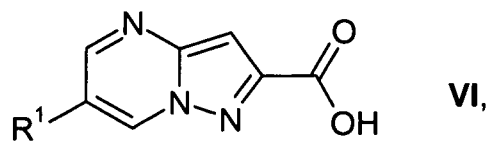
which then is reacted with a compound of Formula IV



to yield a pyrazolopyrimidine compound of Formula V



which is hydrolyzed under acidic conditions to yield a compound of Formula **VI**

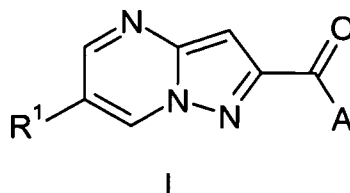


which then is treated with an amine of Formula **VII**



(e.g., in the presence of a condensing agent), to yield a compound of Formula (I), which is converted, if desired, to a pharmaceutically acceptable salt, hydrate, solvate, or polymorph.

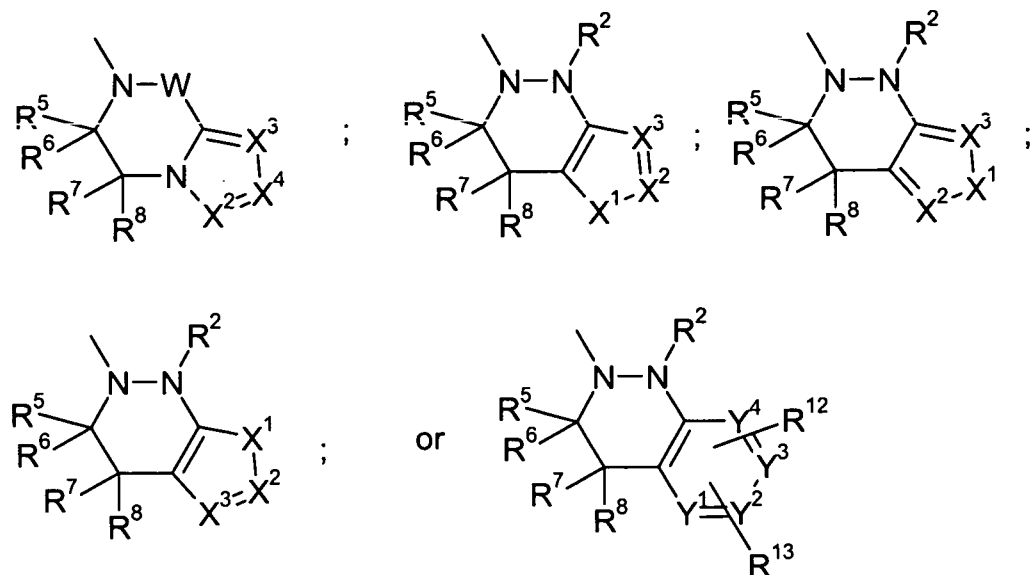
The invention also relates to a further process for the synthesis of a compound selected from those of Formula **I**



wherein

R¹ represents chloro or bromo;

A represents



wherein

W represents NR^2 or CR^3R^4

R^2 represents hydrogen, C_{1-6} alkyl, trifluoromethyl or cyclo C_{3-12} alkyl;

R^3 , R^4 , R^5 , R^6 , which may be the same or different, each independently represent hydrogen, C_{1-6} alkyl, cyclo C_{3-12} alkyl, or trifluoromethyl;

R^7 , and R^8 , which may be the same or different, each independently represent hydrogen, C_{1-6} alkyl, cyclo C_{3-12} alkyl, amino, hydroxy, halogen, or trifluoromethyl;

X^1 represents CR^9R^{10} , NR^{11} , S, or O, and X^2 , X^3 , and X^4 , which may be the same or different each independently represent CR^9 or N, wherein

R^9 and R^{10} , which may be the same or different, each independently represent hydrogen, halogen, amino, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, aryl, C_{1-6} alkyl, cyclo C_{3-12} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, cyclo C_{3-12} alkyloxy, C_{2-6} alkenyloxy, C_{2-6} alkynyloxy, heteroaryl, heterocyclyl, aryloxy, heteroaryloxy, heterocyclyloxy, C_{1-6} alkylamino, di- C_{1-6} alkylamino, cyclo C_{3-12} alkylamino, di-cyclo C_{3-12} alkylamino, N- C_{1-6} alkyl-N-cyclo C_{3-12} alkylamino,

₁₂alkylamino, C₂₋₆alkenylamino, C₂₋₆alkynylamino, di-C₂₋₆alkenylamino, di-C₂₋₆alkynylamino, N-C₁₋₆alkyl-N-C₂₋₆alkenylamino, N-C₁₋₆alkyl-N-C₂₋₆alkynylamino, N-C₂₋₆alkenyl-N-cycloC₃₋₁₂alkylamino, N-C₂₋₆alkynyl-N-cycloC₃₋₁₂alkylamino, N-C₂₋₆alkenyl-N-C₂₋₆alkynylamino arylamino, diarylamino, aryl-C₁₋₆alkylamino, aryl-C₂₋₆alkenylamino, aryl-C₂₋₆alkynylamino, N-aryl-N-cycloC₃₋₁₂alkylamino, heteroarylamino, diheteroarylamino, heteroaryl-C₁₋₆alkylamino, heteroaryl-C₂₋₆alkenylamino, heteroaryl-C₂₋₆alkynylamino, N-heteroaryl-N-cycloC₃₋₁₂alkylamino, N-heteroaryl-N-arylamino, heterocyclylamino, diheterocyclylamino, heterocyclyl-C₁₋₆alkylamino, heterocyclyl-C₂₋₆alkenylamino, heterocyclyl-C₂₋₆alkynylamino, N-heterocyclyl-N-cycloC₃₋₁₂alkylamino, N-heterocyclyl-N-arylamino, N-heterocyclyl-N-heteroarylamino, acyl, acyloxy, acylamino, C₁₋₆alkoxycarbonyl, cycloC₃₋₁₂alkoxycarbonyl, C₂₋₆alkenyloxycarbonyl, C₂₋₆alkynyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, heterocyclilyloxycarbonyl, aminocarbonyl, C₁₋₆alkylaminocarbonyl, di-C₁₋₆alkylaminocarbonyl, cycloC₃₋₁₂alkylaminocarbonyl, di-cycloC₃₋₁₂alkylaminocarbonyl, N-C₁₋₆alkyl-N-cycloC₃₋₁₂alkylaminocarbonyl, C₂₋₆alkenylaminocarbonyl, C₂₋₆alkynylaminocarbonyl, di-C₂₋₆alkenylaminocarbonyl, di-C₂₋₆alkynylaminocarbonyl, N-C₁₋₆alkyl-N-C₂₋₆alkenylaminocarbonyl, N-C₁₋₆alkyl-N-C₂₋₆alkynylaminocarbonyl, N-C₂₋₆alkenyl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-C₂₋₆alkynyl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-C₂₋₆alkenyl-N-C₂₋₆alkynylaminocarbonyl, arylaminocarbonyl, diarylamino, aryl-C₁₋₆alkylaminocarbonyl, aryl-C₂₋₆alkenylaminocarbonyl, aryl-C₂₋₆alkynylaminocarbonyl, N-aryl-N-cyclo C₃₋₇alkylaminocarbonyl, heteroarylaminocarbonyl, diheteroarylaminocarbonyl, heteroaryl-C₁₋₆alkylaminocarbonyl, heteroaryl-C₂₋₆alkenylaminocarbonyl, heteroaryl-C₂₋₆alkynylaminocarbonyl, N-heteroaryl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-heteroaryl-N-arylaminocarbonyl, heterocyclylaminocarbonyl, diheterocyclylaminocarbonyl,

heterocyclyl-C₁₋₆alkylaminocarbonyl, heterocyclyl-C₂₋₆alkenylaminocarbonyl, heterocyclyl-C₂₋₆alkynylaminocarbonyl, N-heterocyclyl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-heterocyclyl-N-arylamino carbonyl, N-heterocyclyl-Nheteroarylamino carbonyl, C₁₋₆alkylsulfinyl, cycloC₃₋₁₂alkylsulfinyl, C₂₋₆alkenylsulfinyl, C₂₋₆alkynylsulfinyl, arylsulfinyl, heteroarylsulfinyl, heterocyclylsulfinyl, C₁₋₆alkylsulfonyl, cycloC₃₋₁₂alkylsulfonyl, C₂₋₆alkenylsulfonyl, C₂₋₆alkynylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heterocyclylsulfonyl, C₁₋₆alkylsulfonylamino, or arylsulfonylamino and

R¹¹ represents hydrogen, C₁₋₆alkyl, cycloC₃₋₁₂alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, acyl, aryl, heteroaryl, heterocyclyl, C₁₋₆alkylaminocarbonyl, di-C₁₋₆alkylaminocarbonyl, C₁₋₆alkylsulfonyl, arylsulfonyl or heteroarylsulfonyl;

Y¹, Y², Y³, and Y⁴ represent C or N, wherein at least two of Y¹, Y², Y³, and Y⁴ represent C;

R¹² and R¹³, which may be the same or different, each independently represent hydrogen, halogen, amino, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, aryl, C₁₋₆alkyl, cycloC₃₋₁₂alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, cycloC₃₋₁₂alkyloxy, C₂₋₆alkenyloxy, C₂₋₆alkynyloxy, heteroaryl, heterocyclyl, aryloxy, heteroaryloxy, heterocyclioxy, C₁₋₆alkylamino, di-C₁₋₆alkylamino, cycloC₃₋₁₂alkylamino, di-cycloC₃₋₁₂alkylamino, N-C₁₋₆alkyl-N-cycloC₃₋₁₂alkylamino, C₂₋₆alkenylamino, C₂₋₆alkynylamino, di-C₂₋₆alkenylamino, di-C₂₋₆alkynylamino, N-C₁₋₆alkyl-N-C₂₋₆alkenylamino, N-C₁₋₆alkyl-N-C₂₋₆alkynylamino, N-C₂₋₆alkenyl-N-cycloC₃₋₁₂alkylamino, N-C₂₋₆alkynyl-N-cycloC₃₋₁₂alkylamino, N-C₂₋₆alkenyl-N-C₂₋₆alkynylamino arylamino, diarylamino, aryl-C₁₋₆alkylamino, aryl-C₂₋₆alkenylamino, aryl-C₂₋₆alkynylamino, N-aryl-N-cycloC₃₋₁₂alkylamino, heteroarylamino, diheteroarylamino, heteroaryl-C₁₋₆alkylamino, heteroaryl-C₂₋₆alkenylamino, heteroaryl-C₂₋₆alkynylamino, N-heteroaryl-N-cycloC₃₋₁₂alkylamino, N-heteroaryl-N-arylamino, heterocyclylamino, diheterocyclylamino, heterocyclyl-C₁₋₆alkylamino,

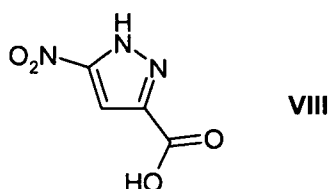
heterocyclyl-C₂₋₆alkenylamino, heterocyclyl-C₂₋₆alkynylamino, N-heterocyclyl-N-cycloC₃₋₁₂alkylamino, N-heterocyclyl-N-arylamino, N-heterocyclyl-N-heteroarylamino, acyl, acyloxy, acylamino, C₁₋₆alkoxycarbonyl, cycloC₃₋₁₂alkoxycarbonyl, C₂₋₆alkenyloxycarbonyl, C₂₋₆alkynyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, heterocyclilyloxycarbonyl, aminocarbonyl, C₁₋₆alkylaminocarbonyl, di-C₁₋₆alkylaminocarbonyl, cycloC₃₋₁₂alkylaminocarbonyl, di-cycloC₃₋₁₂alkylaminocarbonyl, N-C₁₋₆alkyl-N-cycloC₃₋₁₂alkylaminocarbonyl, C₂₋₆alkenylaminocarbonyl, C₂₋₆alkynylaminocarbonyl, di-C₂₋₆alkenylaminocarbonyl, di-C₂₋₆alkynylaminocarbonyl, N-C₁₋₆alkyl-N-C₂₋₆alkenylaminocarbonyl, N-C₁₋₆alkyl-N-C₂₋₆alkynylaminocarbonyl, N-C₂₋₆alkenyl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-C₂₋₆alkynyl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-C₂₋₆alkenyl-N-C₂₋₆alkynylaminocarbonyl, arylaminocarbonyl, diarylamino carbonyl, aryl-C₁₋₆alkylaminocarbonyl, aryl-C₂₋₆alkenylaminocarbonyl, aryl-C₂₋₆alkynylaminocarbonyl, N-aryl-N-cyclo C₃₋₇alkylaminocarbonyl, heteroarylamino carbonyl, diheteroarylamino carbonyl, heteroaryl-C₁₋₆alkylaminocarbonyl, heteroaryl-C₂₋₆alkenylaminocarbonyl, heteroaryl-C₂₋₆alkynylaminocarbonyl, N-heteroaryl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-heteroaryl-N-arylamino carbonyl, heterocyclylaminocarbonyl, diheterocyclylaminocarbonyl, heterocyclyl-C₁₋₆alkylaminocarbonyl, heterocyclyl-C₂₋₆alkenylaminocarbonyl, heterocyclyl-C₂₋₆alkynylaminocarbonyl, N-heterocyclyl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-heterocyclyl-N-arylamino carbonyl, N-heterocyclyl-Nheteroarylamino carbonyl, C₁₋₆alkylsulfinyl, cycloC₃₋₁₂alkylsulfinyl, C₂₋₆alkenylsulfinyl, C₂₋₆alkynylsulfinyl, arylsulfinyl, heteroarylsulfinyl, heterocyclylsulfinyl, C₁₋₆alkylsulfonyl, cycloC₃₋₁₂alkylsulfonyl, C₂₋₆alkenylsulfonyl, C₂₋₆alkynylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heterocyclylsulfonyl, C₁₋₆alkylsulfonylamino, or arylsulfonylamino;

or R¹² and R¹³ together with the two carbon atoms carrying them represent an aryl group which may be optionally substituted by a group selected from halogen, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl, and C₁₋₆alkoxy; a heteroaryl group having 5 or 6 ring members which may be optionally substituted by a group selected from halogen, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl, and C₁₋₆alkoxy; or a heterocyclyl group having 5 or 6

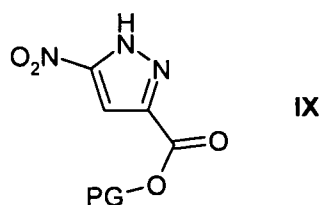
ring members, which may be optionally substituted by a group selected from oxo, halogen, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl, and C₁₋₆alkoxy;

and optical isomers, pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof,

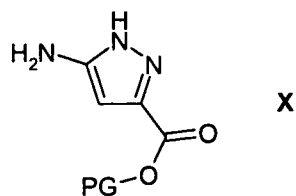
wherein a compound of Formula **VIII**



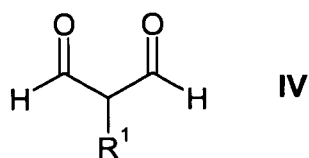
is dissolved in an alcoholic solvent and treated with an esterification facilitator (e.g. thionyl chloride) to yield a compound of Formula **IX**



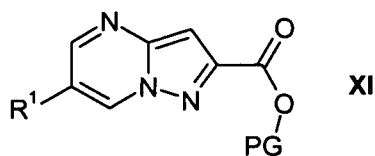
wherein PG represents a protective group, such as a C₁₋₆alkyl group, which is reduced under standard conditions to yield a compound of Formula **X**



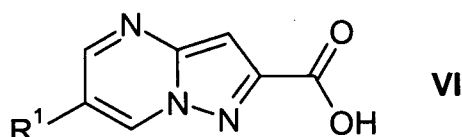
which then is reacted with a compound of Formula **IV**



to yield a pyrazolopyrimidine compound of Formula **XI**



which then is hydrolyzed (e.g., under under acidic conditions) to yield a compound of Formula **VI**



which then is treated with an amine of Formula **VII**



(e.g., in the presence of a condensing agent), to yield a compound of Formula **I**, which is converted, if desired, to a pharmaceutically acceptable salt, hydrate, solvate, or polymorph.

DETAILED DESCRIPTION OF THE INVENTION

For the purpose of the present invention, in the compounds of Formula **I** the carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_{i-j} indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, for example, (C₁₋₃)alkyl refers to alkyl of one to three carbon atoms (i.e. 1, 2 or 3 carbon atoms), inclusive, (methyl, ethyl, propyl, and isopropyl), straight and branched forms thereof, (C₁₋₆) for instance refers to a radical of one to six carbon atoms (i.e. 1, 2, 3, 4, 5 or 6 carbon atoms).

As used herein, the following definitions are applicable unless otherwise described, the term "C₁₋₆alkyl" represents straight or branched chain alkyl groups which may be

optionally substituted by one or more substituents selected from halogen, trifluoromethyl, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino. Examples of such alkyl groups include methyl, ethyl, n-propyl, 2-propyl, n-butyl, tert-butyl, -CF₃, -C₂F₅, -CBr₃ and -CCl₃.

The term "C₂₋₆alkenyl" represents straight or branched chain alkenyl groups. The term "C₁₋₆alkoxy" represents straight or branched chain -O-C₁₋₆alkyl groups which may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, amino, hydroxy, C₁₋₆alkylamino and di-(C₁₋₆alkyl)amino. Examples of such alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, -OCF₃ and -OC₂F₅.

The term "cycloC₃₋₁₂alkyl" represents monocyclic or bicyclic, or tricyclic alkyl groups, including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptyl and adamantanyl, which may be optionally substituted by one or more substituents, which may be the same or different, selected independently from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, amino, hydroxy, nitro, cyano, cyanomethyl, C₁₋₆alkoxycarbonyl, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonylamino, and C₁₋₆alkylenedioxy.

The term "aryl" represents phenyl or naphthyl, wherein the phenyl or naphthyl group is optionally substituted by one or more substituents, which may be the same or different, selected independently from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, amino, hydroxy, nitro, cyano, cyanomethyl, C₁₋₆alkoxycarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkylamino, di-(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonylamino, aminocarbonyl, N-C₁₋₆alkylaminocarbonyl, di-N,N-C₁₋₆alkylaminocarbonyl, pyrrolidinyl, piperidinyl, morpholinyl, and piperazinyl, cycloC₃₋₁₂alkyl or optionally C₁₋₆alkylenedioxy.

The term "heteroaryl" represents an aromatic 5-6 membered ring containing from one to four heteroatoms selected from oxygen, sulfur and nitrogen, or a bicyclic group comprising a 5-6 membered ring containing from one to four heteroatoms selected from oxygen, sulfur and nitrogen fused with a benzene ring or a 5-6

membered ring containing from one to four heteroatoms selected from oxygen, sulfur and nitrogen, wherein the heteroaryl group may be optionally substituted by one or more substituents, which may be the same or different, selected independently from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, amino, hydroxy, nitro, cyano, C₁₋₆alkoxycarbonyl, C₁₋₆alkoxycarbonyloxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonylamino, aminocarbonyl, N-C₁₋₆alkylaminocarbonyl, di-N,N-C₁₋₆alkylaminocarbonyl, pyrrolidinyl, piperidinyl, morpholinyl, cycloC₃₋₁₂alkyl, C₁₋₆alkylenedioxy and aryl. Representative heteroaryl groups include furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, pyrazolyl, triazolyl, thiadiazolyl, thiazolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, purinyl, pyrazolyl, benzofuryl, benzothienyl, indolyl, indoliziny, isoindolyl, indolinyl, indazolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, isoquinolinyl, quinoliziny, phthalazinyl, theridinyl.

The term "heterocyclyl" represents a saturated or unsaturated non-aromatic 3 to 12 membered ring comprising one to four heteroatoms selected from oxygen, sulfur and nitrogen, and a saturated or unsaturated non-aromatic bicyclic ring system having 3 to 12 members comprising one to six heteroatoms selected from oxygen, sulfur and nitrogen, wherein the heterocyclic ring or ring system is optionally substituted by one or more substituents selected independently from a halogen, trifluoromethyl, C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, amino, hydroxy, nitro, cyano, C₁₋₆alkoxycarbonyl, C₁₋₆alkylamino, di-C₁₋₆alkylamino, pyrrolidinyl, piperidinyl, morpholinyl, pyridinyl, and aryl; examples of such heterocyclyl groups include piperidinyl, morpholinyl, thiomorpholinyl, imidazoliny, imidazolidinyl, pyrazoliny, pyrazolidinyl, pyrroliny, pyrrolidinyl, or piperaziny, wherein the heterocyclic ring or ring system is linked to the group to which it is attached optionally via nitrogen or a carbon atom.

The term "acyl" includes C₁₋₆alkylcarbonyl, cycloC₃₋₁₂alkylcarbonyl, C₂₋₆alkenylcarbonyl, C₂₋₆alkynylcarbonyl, arylcarbonyl, arylC₁₋₆alkylcarbonyl, heteroarylcarbonyl and heterocyclylcarbonyl, wherein the terms alkyl, aryl,

heteroaryl, and heterocyclyl are defined as above. Examples are acetyl, propionyl, benzoyl or pivaloyl.

The term "halogen" represents fluorine, chlorine, bromine and iodine.

The compounds of the present invention are usually named according to the IUPAC or CAS nomenclature system. Abbreviations which are well known to one of ordinary skill in the art may be used (e.g. "Ph" for phenyl, "Me" for methyl, "Et" for ethyl, "h" for hour or hours, and "rt" for room temperature).

The term "analog" or "derivative" is used herein in the conventional pharmaceutical sense, to refer to a molecule that structurally resembles a reference molecule, but has been modified in a targeted and controlled manner to replace one or more specific substituents of the referent molecule with an alternate substituent, thereby generating a molecule which is structurally similar to the reference molecule. Synthesis and screening of analogs (e.g., using structural and/or biochemical analysis), to identify slightly modified versions of a known compound which may have improved or biased traits (such as higher potency and/or selectivity at a specific targeted receptor type, greater ability to penetrate blood-brain barriers, fewer side effects, etc.) is a drug design approach that is well known in pharmaceutical chemistry.

In addition, using methods known to those skilled in the art, analogs and derivatives of the compounds of the invention can be created which have improved therapeutic efficacy, i.e., higher potency and/or selectivity at a specific targeted receptor type, either greater or lower ability to penetrate mammalian blood-brain barriers (e.g., either higher or lower blood-brain barrier permeation rate), fewer side effects, etc.

The phrase "pharmaceutically acceptable", as used in connection with compositions of the invention, refers to molecular entities and other ingredients of such compositions that are physiologically tolerable and do not typically produce untoward reactions when administered to a mammal (e.g., human). Preferably, as used herein, the term "pharmaceutically acceptable" means approved by a regulatory

agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in mammals, and more particularly in humans.

Compounds of the present invention may be in the form of pharmaceutically acceptable salts. "Pharmaceutically acceptable salts" refers to those salts which possess the biological effectiveness and properties of the parent compound and which are not biologically or otherwise undesirable. The nature of the salt is not critical, provided that it is non-toxic and does not substantially interfere with the desired pharmacological activity.

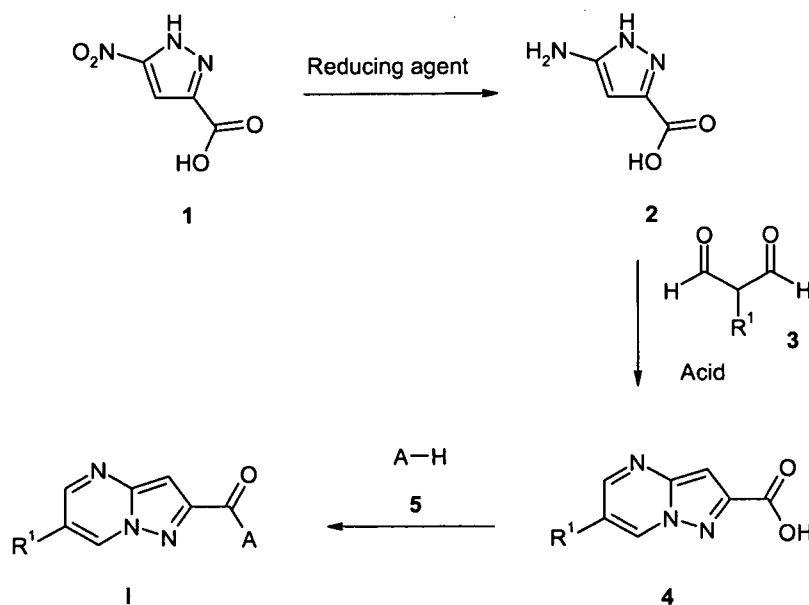
It will be appreciated by those skilled in the art that compounds of the invention having a chiral center may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically active, polymorphic, tautomeric, or stereoisomeric form, or mixture thereof, of a compound of the invention, which possesses the useful properties described herein.

All patents, applications, publications, test methods, literature, and other materials cited in this application are hereby incorporated by reference.

The following Schemes 1-3 describe the preparation of compounds of Formula I of the present invention. All of the starting materials may be prepared by procedures described in these schemes, by procedures well known to one of ordinary skill in organic chemistry, or may be obtained commercially. All of the final compounds of the present invention may be prepared by procedures described in these charts or by procedures analogous thereto, which would be well known to one of ordinary skill in organic chemistry. All of the variables used in the schemes are as defined below or as in the claims. The compounds containing one or more chiral centers can be prepared as racemates or mixtures of various stereoisomers and then separated. However, they also can be prepared by a special enantioselective synthesis. For several of the chiral compounds, the enantiomers differ in pharmacological activity.

Compounds of the present invention may be synthesized according to Scheme 1.

5-Nitro-1H-pyrazole-3-carboxylic acid **1** is reduced under standard conditions, such as treatment with hydrogen in the presence of palladium(0) on carbon in a solvent such as methanol, to yield 5-amino-1H-pyrazole-3-carboxylic acid **2**. Compound **2** is reacted with di-aldehyde **3**, carrying a bromo or chloro substituent at the R¹ position, under acid conditions, such as acetic acid, at elevated temperatures to give 6-bromo- or 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (**4**). A compound of Formula **I** is prepared from **4** via reaction with an appropriate secondary amine **5** in the presence of a condensation agent, including, for example, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate ("TBTU") or N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (EDC).

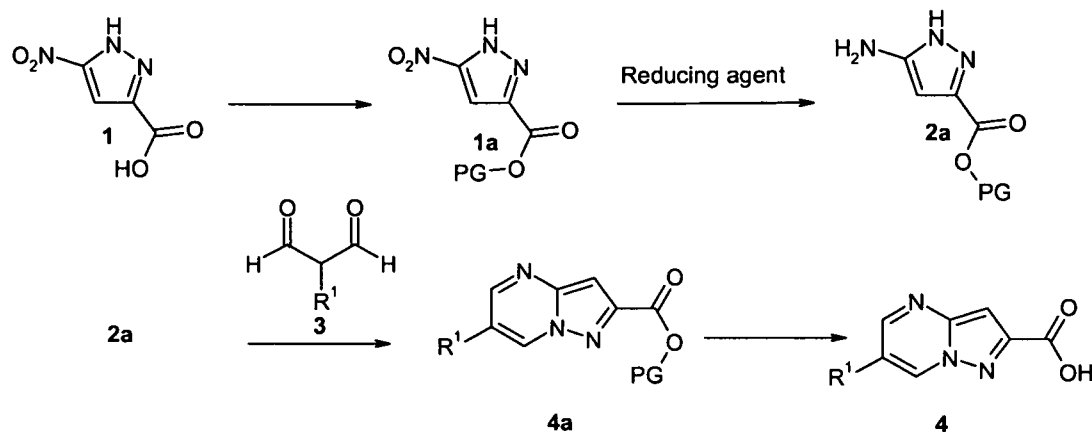


Scheme 1: General procedure towards compounds of Formula I.

The amines (**5**) are commercially available or may be prepared according to literature procedures (see, for example, Bull. Soc. Chim. Belg., v.71, 1962; p. 592; US 2002/049223 A1 (2002/04/25); Chem. Ber., 84, 1951, p. 795-798; Bull. Soc. Chim. Fr.5, 4, 1937, p. 1265-1269; Zh. Obshch. Khim., 7, 1937, p. 1999-2004; Chem. Pharm. Bull., EN, 31, 8, 1983, p. 2583-2592; Tetrahedron, 28, 1972, p. 5999-6004; J. Org. Chem., 34, 8, 1969, p. 2478; Pharm. Chem. J. (Engl. Tran.); 5; 5;

1971, p. 260; Khfzan; Khim.Farm.Zh., 5, 5, 1971, p. 13; J. Chem. Soc., 1965, p. 5391-5401; Zh. Organi. Khimii, 22, 1986, p. 2610-2614).

Compound **4** may also be prepared according to Scheme 2.

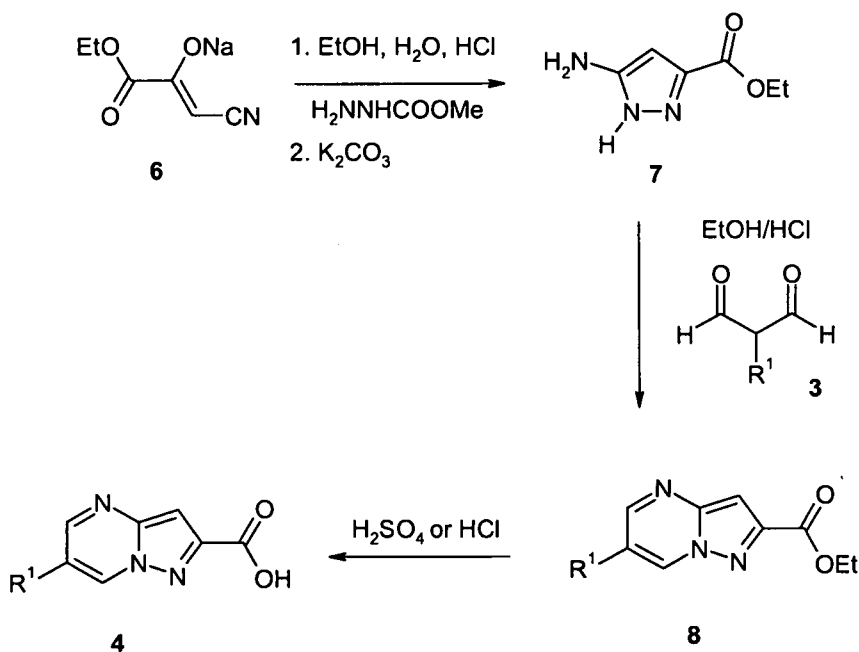


Scheme 2: General procedure towards Compound **4**.

5-Nitro-3-pyrazole carboxylic acid **1** is dissolved in an alcoholic solvent, e.g. methanol or ethanol, and reacted with thionyl chloride to give compound **1a** bearing an alkyl ester group. The term "PG" denotes any C₁₋₆alkyl chain, including branched alkyl chains, for example, methyl and ethyl groups. 5-Nitro-3-pyrazole-carboxylic acid alkyl ester **1a** is reduced under standard conditions, such as treatment with hydrogen in the presence of palladium(0) on carbon in a solvent such as methanol, to yield 5-amino-1H-pyrazole-3-carboxylic acid alkyl ester **2a**. Compound **2a** is reacted with di-aldehyde **3**, carrying a bromo or chloro substituent at the R¹ position, under acid conditions, such as acetic acid, at elevated temperatures to give 6-bromo- or 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid alkyl ester (**4a**). The ester **4a** is hydrolyzed under acidic conditions such as sulphuric acid (30%) to yield 6-bromo- or 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid **4**. A compound of Formula **I** is prepared from **4** via reaction with an appropriate secondary amine **5** as shown in Scheme 1.

Compound **4** may also be prepared according to Scheme 3.

Ethyl 3-cyano-2-oxopropionate sodium salt ("NaCOPE") **6** is treated with methyl hydrazino formiate to yield ethyl 5-aminopyrazole-3-carboxylate **7**. Compound **7** is reacted with dialdehyde **3**, carrying a bromo or chloro substituent at the R¹ position, under acidic conditions, to yield ethyl 6-bromo- or 6-chloro-pyrazolo[1,5a]pyrimidine-2-carboxylate **8**. The ester **8** is hydrolyzed under acidic conditions to yield 6-bromo- or 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid **4**. A compound of Formula I is prepared from **4** via reaction with an appropriate secondary amine **5** as shown in Scheme 1.



Scheme 3: General procedure towards Compound **4**.

It will be appreciated that in the above transformations it may be necessary or desirable to protect any sensitive groups in the molecule of the compound in question in order to avoid undesirable side reactions.

The pure stereoisomeric forms (including optical isomers) of the compounds and the intermediates of this invention may be obtained by the application of art-known procedures. Diastereomers may be separated by physical separation methods such as selective crystallization and chromatographic techniques, e.g. liquid chromatography

using chiral stationary phases. Enantiomers (optically active isomers) may be separated from each other by selective crystallization of their diastereomeric salts with optically active acids. Alternatively, enantiomers may be separated by chromatographic techniques using chiral stationary phases.

Said pure stereoisomeric forms may also be derived from the corresponding pure stereoisomeric form of appropriate starting materials, provided that the reaction occur stereoselectively. Stereoisomeric forms of Formula I are included within the scope of this invention.

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 and purification of pharmaceutically acceptable compounds. All salts whether pharmaceutically acceptable or not are included within the ambit of the present invention.

The pharmaceutically acceptable salts as mentioned above are meant to comprise the therapeutically active non-toxic salt forms, which the compounds of Formula I are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acids as inorganic acids, e.g. hydrohalic acids such as hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids such as acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, oxopropanoic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfonic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely, the salt form can be converted by treatment with alkali into the free base form.

Pharmaceutical Compositions

The active ingredients of Formula I of the invention, together with one or more excipient/s like adjuvants, carriers, or diluents, may be placed into the form of

pharmaceutical compositions, unit dosages or dosage forms. The pharmaceutical compositions may be employed as solid dosage forms, such as powders, granules, pellets, coated or uncoated tablets or filled capsules, or liquid dosage forms, such as solutions, suspensions, emulsions, or capsules filled with the same, or semi solid dosage forms, such as gels, creams and ointments. The active ingredient(s) dissolution and release profiles of the pharmaceutical dosage forms can be varied from seconds to months.

The pharmaceutical compositions are designed for the use in animals and humans and can be applied via all application routes. Preferred application routes will be the oral route, the dermal route, the pulmonary route, the nasal route, the rectal route, the parenterale route. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional or new ingredients in conventional or special proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. Tablets containing one (1) to one hundred (100) milligrams of active ingredient or, more broadly, zero point five (0.5) to five hundred (500) milligrams per tablet, are accordingly suitable representative unit dosage forms.

The term "carrier" applied to pharmaceutical compositions of the invention refers to a diluent, excipient, or vehicle with which an active compound is administered. Such pharmaceutical carriers can be sterile liquids, such as water, saline solutions, aqueous dextrose solutions, aqueous glycerol solutions, and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. A.R. Gennaro, 20th Edition, describes suitable pharmaceutical carriers in "Remington: The Science and Practice of Pharmacy".

Method of treating and pharmaceutical formulations

Due to their high degree of activity and their low toxicity, together presenting a most favorable therapeutic index, the active principles of Formula I of the invention may be administered to a subject, e.g., a living animal (including a human) body, in need

thereof, for the treatment, alleviation, or amelioration, palliation, or elimination of an indication or condition which is susceptible thereto, or representatively of an indication or condition set forth elsewhere in this application, preferably concurrently, simultaneously, or together with one or more pharmaceutically-acceptable excipients, carriers, or diluents, especially and preferably in the form of a pharmaceutical composition thereof, whether by oral, rectal, or parental (including intravenous and subcutaneous) or in some cases even topical route, in an effective amount. Suitable dosage ranges are 1-1000 milligrams daily, preferably 10-500 milligrams daily, and especially 50-500 milligrams daily, depending as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and the preference and experience of the physician or veterinarian in charge.

The term "treat" is used herein to mean to relieve or alleviate at least one symptom of a disease in a subject. Within the meaning of the present invention, the term "treat" also denotes to arrest, delay the onset (*i.e.*, the period prior to clinical manifestation of a disease) and/or reduce the risk of developing or worsening a disease.

The term "therapeutically effective" applied to dose or amount refers to that quantity of a compound or pharmaceutical composition that is sufficient to result in a desired activity upon administration to a living animal body in need thereof.

The active agents of Formula I of the present invention may be administered orally, topically, parenterally, or mucosally (e.g., buccally, by inhalation, or rectally) in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers. It is usually desirable to use the oral route. The active agents may be administered orally in the form of a capsule, a tablet, or the like (see Remington: The Science and Practice of Pharmacy, 20th Edition). The orally administered pharmaceutical compositions may be administered in the form of a time-controlled release vehicle, including diffusion-controlled systems, osmotic devices, dissolution-controlled matrices, and erodible/degradable matrices.

For oral administration in the form of a tablet or capsule, the active drug component of Formula I may be combined with a non-toxic, pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, sucrose, glucose, mannitol, sorbitol and other reducing and non-reducing sugars, microcrystalline cellulose, calcium sulfate, or calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc, or silica, steric acid, sodium stearyl fumarate, glyceryl behenate, calcium stearate, and the like); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate), coloring and flavoring agents, gelatin, sweeteners, natural and synthetic gums (such as acacia, tragacanth or alginates), buffer salts, carboxymethylcellulose, polyethyleneglycol, waxes, and the like. For oral administration in liquid form, the drug components may be combined with non-toxic, pharmaceutically acceptable inert carriers (e.g., ethanol, glycerol, water), suspending agents (e.g., sorbitol syrup, cellulose derivatives or hydrogenated edible fats), emulsifying agents (e.g., lecithin or acacia), non-aqueous vehicles (e.g., almond oil, oily esters, ethyl alcohol or fractionated vegetable oils), preservatives (e.g., methyl or propyl-p-hydroxybenzoates or sorbic acid), and the like. Stabilizing agents such as antioxidants (BHA, BHT, propyl gallate, sodium ascorbate, citric acid) may also be added to stabilize the dosage forms.

The tablets containing as active compound a compound of Formula I may be coated by methods well known in the art. The compositions of the invention containing as active compound a compound of Formula I may be also introduced in beads, microspheres or microcapsules, e.g., fabricated from polyglycolic acid/lactic acid (PGLA). Liquid preparations for oral administration may take the form of, for example, solutions, syrups, emulsions or suspensions, or they may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Preparations for oral administration may be suitably formulated to give controlled or postponed release of the active compound.

The active drugs of Formula I may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines, as is well known.

Drugs of the invention containing as active compound a compound of Formula I may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. Active drugs may also be coupled with soluble polymers as targetable drug carriers. Such polymers include polyvinylpyrrolidone, pyran copolymer, polyhydroxy-propyl methacrylamide-phenol, polyhydroxy-ethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, active drug may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxybutyric acid, polyorthoesters, polyacetals, polyhydropyrans, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogels.

For administration by inhalation, the therapeutics according to the present invention containing as active compound a compound of Formula I may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra-fluoroethane, carbon dioxide, or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin for use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The formulations of the invention containing a compound of Formula I may be delivered parenterally, i.e., by intravenous (i.v.), intracerebroventricular (i.c.v.), subcutaneous (s.c.), intraperitoneal (i.p.), intramuscular (i.m.), subdermal (s.d.), or intradermal (i.d.) administration, by direct injection, via, for example, bolus injection or continuous infusion. Formulations for injection can be presented in unit

dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions can take such forms as excipients, suspensions, solutions, or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient can be in powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

Compositions of the present invention containing a compound of Formula I may also be formulated for rectal administration, e.g., as suppositories or retention enemas (e.g., containing conventional suppository bases such as cocoa butter or other glycerides).

The compositions containing a compound of Formula I may, if desired, be presented in a pack or dispenser device, which may contain one or more unit dosage forms containing the active ingredient and/or may contain different dosage levels to facilitate dosage titration. The pack may, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. Compositions of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

As disclosed herein, the dose of the components in the compositions of the present invention is determined to ensure that the dose administered continuously or intermittently will not exceed an amount determined after consideration of the results in test animals and the individual conditions of a patient. A specific dose naturally varies depending on the dosage procedure, the conditions of a patient or a subject animal such as age, body weight, sex, sensitivity, feed, dosage period, drugs used in combination, seriousness of the disease. The appropriate dose and dosage times under certain conditions can be determined by the test based on the above-described indices but may be refined and ultimately decided according to the judgment of the practitioner and each patient's circumstances (age, general condition, severity of symptoms, sex, etc.) according to standard clinical techniques.

determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between therapeutic and toxic effects is the therapeutic index and it may be expressed as the ratio LD₅₀/ED₅₀. Compositions that exhibit large therapeutic indices are preferred.

EXPERIMENTAL PART

The compounds and their preparation of the present invention will be better understood in connection with the following examples, which are intended as an illustration of and not a limitation upon the scope of the invention.

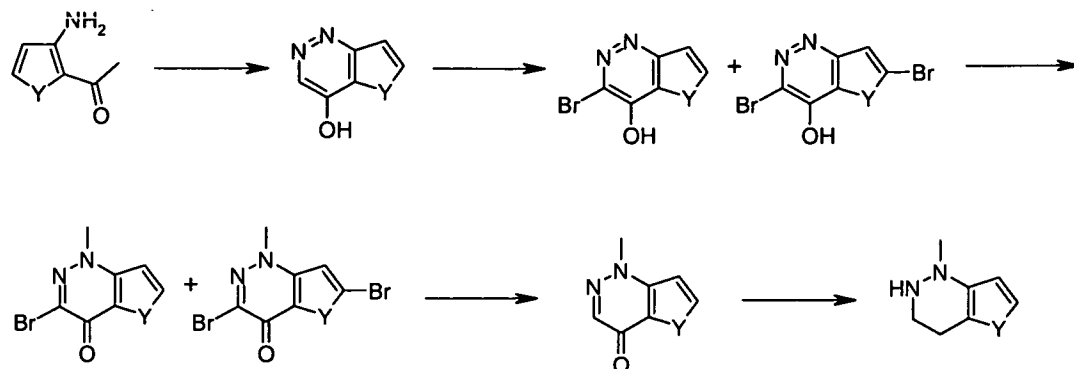
Hereinafter, "DMF" is defined as N,N-dimethylformamide, "THF" as tetrahydrofuran, "HCl" as hydrochloric acid, "NaOH" as sodium hydroxide, "MeOH" as methanol, "DMSO" as dimethylsulfoxide and "TBTU" as O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate.

In order to prepare the amine component of the pyrazolopyrimidine compounds of formula (I) the following General Schemes can be used:

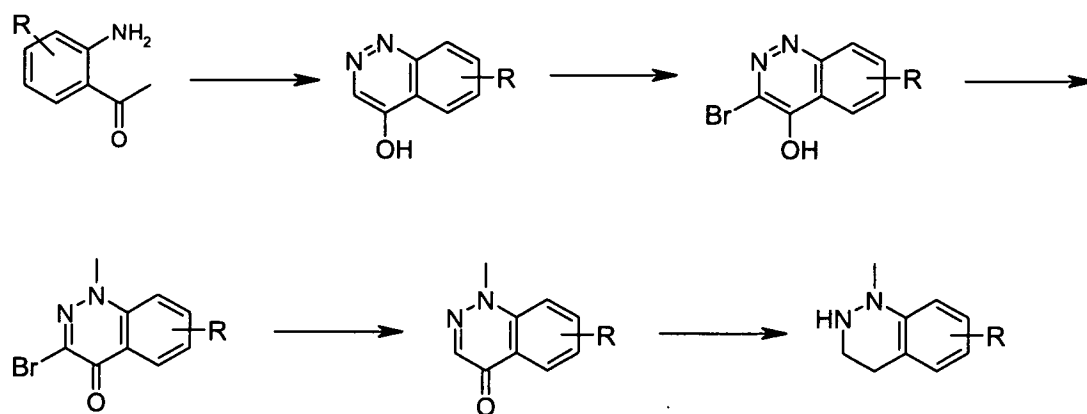
General Scheme 1



General Scheme 2

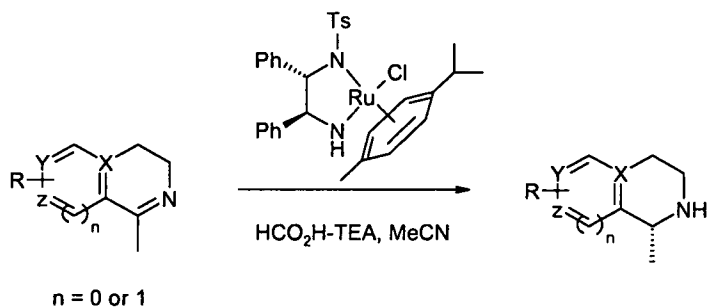


General Scheme 3



There are several routes for the synthesis of chiral pyrazolopyrimidines which are outlined in the following:

A) Enantiomer synthesis by asymmetric transfer hydrogenation of bicyclic imines using a chiral ruthenium catalyst:

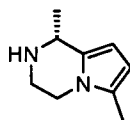


Asymmetric transfer hydrogenation of 1-methyl-3,4-dihydro-isoquinoline

Preparation of catalyst.

A mixture of $[\text{RuCl}_2(\eta^6\text{-p-cymene})]_2$ (1.53 g, 2.5 mmol), (1S, 2S)-*N*-p-toluenesulfonyl-1,2-diphenylethylenediamine (1.83 g, 5.0 mmol) and triethylamine (1.4 mL, 10 mmol) in 2-propanol (50 mL) was heated at 80°C for 1h. The orange solution was concentrated to 1/3 of volume and the precipitate was collected by filtration, washed with small amount of water to give $\text{RuCl}[(1S, 2S)\text{-p-TsNCHPhCHPhNH}_2](\eta^6\text{-p-cymene})$ (2.99 g, 94%) as an air-stable orange solid.

Transfer hydrogenation.



1,6-Methyl-3,4-dihydropyrrolo[1,2-a]pyrazine (2.0 gr, 13.5 mmol, 1.0 equiv.) was dissolved in a mixture of acetonitrile (5 ml) and triethylammonium formate (2:5) azeotrope (5 ml). Ruthenium catalyst $[\text{RuCl}[(1S, 2S)\text{-p-TsNCHPhCHPhNH}_2](\eta^6\text{-p-cymene})]$ (219 mg, 2.5 mol%) was added and the red reaction mixture was stirred at room temperature for 24 hours. The mixture was quenched with saturated NaHCO_3 solution and extracted with DCM (3x). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated to dryness to yield 2.00 gr (99%) of the title product.

LC-MS m/z 150 (MH^+)

B) Separation via Chiral Column Chromatography

In the following, specific compounds according to the invention are described in more detail:

Building Block Syntheses:

1-Methyl-3,4-dihydro-pyrrolo[1,2-a]pyrazine

Conc. HCl (8.8 ml) and water (10 ml) are carefully added to ethylene diamine (20 g, 0.33 mol) at stirring and ice bath cooling followed by addition of 2-acetylfuran (16 g, 0.145 mol). The mixture is refluxed for 15 min, then stirred without heating for 1 h, saturated with K_2CO_3 and extracted with dichloromethane (3x50 ml). The combined extracts are washed with 30% K_2CO_3 solution (30 ml), dried over K_2CO_3 and evaporated. The residue is distilled (b.p. 90-92°C/1 mm) to give the title compound. The yield is 12 g (61%).

m/z (APCI+) 135 ($M+H^+$)

1-Methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine

$NaBH_4$ (1g, 26.3 mmol) is added portionwise to the solution of 1-methyl-3,4-dihydropyrrolo[1,2-a]pyrazine (2.68 g, 20 mmol) in methanol (15 ml) and the mixture is stirred for 1 h at r.t. and evaporated. The residue is dissolved in water (10 ml) and extracted with dichloromethane (3x20 ml). The combined extracts are dried over K_2CO_3 and evaporated. The residue is purified by column chromatography on silica gel (eluent: chloroform-ethanol 0→5%) to give the title compound. The yield is 0.95 g (35%).

1,6-Dimethyl-3,4-dihydro-pyrrolo[1,2-a]pyrazine

Conc. HCl (8.8 ml) and water (10 ml) are carefully added to ethylene diamine (43 g, 0.725 mol) at stirring and ice-bath cooling followed by addition of 5-methyl-2-acetylfuran (30 g, 0.242 mol). The mixture is refluxed for 15 min, then stirred without heating for 1 h and extracted with dichloromethane (2x50 ml). The combined extracts are washed with water (40 ml), dried over K_2CO_3 and evaporated. The residue is distilled (b.p. 97°C/1 mm) to give the title compound. The yield is 30 g (70%).

m/z (APCI+) 149 ($M+H^+$)

1,6-Dimethyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine

NaBH₄ (1g, 26.3 mmol) is added portionwise to a solution of 1,6-dimethyl-3,4-dihydropyrrolo[1,2-a]pyrazine (3 g, 20.2 mmol) in methanol (15 ml) and the mixture is stirred for 1 h at r.t. and evaporated. The residue is dissolved in water (10 ml) and extracted with dichloromethane (2x20 ml). The combined extracts are dried over K₂CO₃ and evaporated. The residue is purified by column chromatography on silica gel (eluent: chloroform-ethanol 0→5%) to give the title compound. The yield is 2.3 g (78%).

N,N-Dibenzyl-*N*-[2-(1*H*-1,2,3-triazol-1-yl)ethyl]amine

N-(2-Chloroethyl) dibenzylamine hydrochloride (1.0 g, 3.38 mmol, 1.0 equiv) is suspended in *t*-butanol (25 mL). Added as followed 1,2,3-1*H*-triazole (391 µl, 6.75 mmol, 2.0 equiv), KI (561 mg, 3.38 mmol, 1.0 equiv), LiCl (286 mg, 6.75 mmol, 2.0 equiv) and NaOtBu (975 mg, 10.1 mmol, 3.0 equiv). The resulting mixture is heated to 90°C for 4 h. Water (40 mL) is added and the mixture is extracted twice with toluene (40 mL). The organic layer is washed sequentially with water (40 mL) and brine (40 mL), dried over Na₂SO₄, filtered off and concentrated in vacuo. The residue is purified by flash column chromatography, (10 to 50% ethyl acetate in heptane) to provide 300 mg (30%) of the title compound.

LC-MS *m/z* 293 (MH⁺); ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 1.26, 1.71, 2.95, 6.62, 4.38, 7.21-7.29, 7.38, 7.65.

N-Methoxy-*N*-methyl-acetamide

Acetic acid (2.47 mL, 42.8 mmol, 1.0 equiv) and *N*,*O*-dimethyl-hydroxylamine hydrochloride (4.60 g, 47.1 mmol, 1.1 equiv) are dissolved in dichloromethane (400 mL) and the mixture is cooled in an ice bath. Triethylamine (6.62 mL, 47.1 mmol, 1.1 equiv), EDCI (9.03 g, 47.1 mmol, 1.1 equiv) and HOAt (0.583 g, 4.28 mmol, 0.1 equiv) are added. The resulting mixture is stirred overnight at room temperature under nitrogen atmosphere. The mixture is successively washed with 1N HCl solution (150 mL), sat. NaHCO₃ solution (150 mL) and brine (100 mL), dried over Na₂SO₄, filtered off and concentrated in vacuo, co-evaporation with diethyl ether to yield 2.38 g (54%) of the title compound as a colorless oil.

GC-MS m/z 103; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) 2.13, 3.18, 3.70.

1-[3-(2-Dibenzylamino-ethyl)-3H-[1,2,3]triazol-4-yl]-ethanone

N,N-Dibenzyl-*N*-[2-(1*H*-1,2,3-triazol-1-yl)ethyl]amine (300 mg, 1.03 mmol, 1.0 equiv) is dissolved in THF (23 mL) and cooled to -78°C . 1.6M *n*-BuLi solution in hexane (0.79 mL, 1.26 mmol, 1.2 equiv) is slowly added and stirred for 1.5 hour. This gave a clear grey solution. At -78°C a solution of *N*-methoxy-*N*-methylacetamide (127 mg, 1.26 mmol, 1.2 equiv) in THF (2 mL) is added. The resulting mixture is stirred at room temperature for 2 h. Water (10 mL) is added and the mixture is concentrated in vacuo. An additional portion of water is added and the aqueous mixture is extracted twice with diethyl ether. The combined organic layers are washed with brine, dried over Na_2SO_4 and evaporated. The residue is purified by flash column chromatography, (20 to 50% ethyl acetate in heptane) to yield 147 mg (43%) of the title compound as a white solid.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) 2.29, 2.85, 3.56, 4.80, 7.14-7.26, 8.04.

4-Methyl-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazine

1-[3-(2-Dibenzylamino-ethyl)-3H-[1,2,3]triazol-4-yl]-ethanone (50 mg, 0.150 mmol, 1.0 equiv) is dissolved in ethanol (20 mL). Pd/C (10 mg, cat.) is added and placed under hydrogen atmosphere using a balloon. The resulting mixture is stirred at room temperature for 2 h. The reaction mixture is flushed with nitrogen. The mixture is filtered off over kieselguhr, rinsed with ethyl acetate and concentrated in vacuo to give 20 mg (95%) of the title compound as an colorless oil.

GC-MS m/z 139; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) 1.49, 1.66, 3.18-3.25, 3.46-3.51, 4.13-4.28, 4.43-4.48, 7.47.

6-Chloro-1-methyl-3,4-dihydro-pyrrolo[1,2-*a*]pyrazine

N-Chlorosuccinimide (8.42 gr, 63.1 mmol, 2.1 equiv.) is added to a cooled ($<-5^\circ\text{C}$) solution of 1-methyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine (4.09 gr, 30.0 mmol, 1.0 equiv.) in DCM (80 ml). After addition the mixture is stirred for 30 minutes. A

30% NaOH solution (40 ml) is added and the mixture is stirred vigorously for 1 hour at room temperature. The layers are separated and the aqueous layer is extracted with DCM (2x). The combined organic extracts are dried over Na₂SO₄ and concentrated. The residue is purified by flash column chromatography (Aluminium oxide, 20% EtOAc in heptane to 100% EtOAc) to afford 0.4 gr of product as a brown oil.

Flushing the column with 5% MeOH in DCM afforded more material; total yield: 4.16 gr (yield: 65% corrected for purity).

Purity: ~80%, contains product and some baseline material (Alumina, 50% Heptane in EtOAc).

LC-MS m/z 169 (MH⁺); ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 2.39, 3.89-3.98, 6.19-6.20, 6.62-6.63.

Cinnolin-4-ol

A mixture of 2'-aminoacetophenone (21 g, 0.155 mol) in concentrated HCl (105 mL) is cooled to -5°C. A solution of sodium nitrite (11.8 g, 0.171 mol) in water (32 mL) is added slowly maintaining the temperature below 0°C. After that the mixture is stirred at 65°C for 3 h. The mixture is cooled to room temperature. The precipitate is filtered off, washed with ether, dried and dissolved in water (minimal amount). Sodium hydrocarbonate (8 g) is carefully added to the solution, the mixture is stirred for 1 h and filtered. The precipitate is washed with water and dried on air to give 7.47 g (33%) of the title compound.

m/z (APCI⁺) 147 (M+H⁺)

3-Bromo-cinnolin-4-ol

A solution of bromine (4.01 mL, 78 mmol) in glacial acetic acid (24 mL) is carefully added within 30 min to refluxing mixture of cinnolin-4-ol (11.4 g, 78 mmol), potassium acetate (7.73 g, 79 mmol) and glacial acetic acid (105 mL). After that the reaction mixture is refluxed for 45 min, cooled to room temperature and poured into ice water (500 mL). Formed yellow precipitate is filtered off, washed with water, dried on air to give 13.1 g (75%) of the title compound.

m/z (APCI+) 224, 226 ($M+H^+$)

3-Bromo-1-methyl-1H-cinnolin-4-one

Potassium tert-butoxide (6.0 g, 53.2 mmol) is added to a suspension of 3-bromo-cinnolin-4-ol (8.0 g, 35.6 mmol) in dry tetrahydrofuran (180 mL), then methyl iodide (3.54 mL, 42.8 mmol) is added hereto. Then the reaction mixture is refluxed for 16 h, cooled to room temperature, diluted with water (500 mL) and extracted with dichloromethane (2×200 mL). The combined organic extracts are dried over sodium sulfate and evaporated. The residue is purified by column chromatography on silica gel (eluent: ethyl acetate-hexane 50 to 70%) to obtain 5.96 g (70%) of the title compound.

m/z (APCI+) 238, 240 ($M+H^+$)

1-Methyl-1H-cinnolin-4-one

A suspension of 3-bromo-1-methyl-1H-cinnolin-4-one (5.9 g, 24.7 mmol), 10% Pd/C (0.5 g) and triethylamine (25 mL) in ethanol (150 mL) is stirred under hydrogen atmosphere for 4 h. The mixture is filtered, the filtrate is evaporated. The residue is partitioned between dichloromethane and water. The organic layer is washed with water, dried over sodium sulfate and evaporated to give 3.55 g (90%) of the title compound.

m/z (APCI+) 161 ($M+H^+$)

1-Methyl-1,2,3,4-tetrahydro-cinnoline

A solution of 1-methyl-1H-cinnolin-4-one (2.0 gr, 12.5 mmol, equiv) in toluene (100 mL) is treated with 4N LiAlH₄ in Et₂O (7.8 mL, 31.2 mmol, 2.5 equiv) and refluxed for 4 hrs. After cooling to room temp., another batch of LiAlH₄ (7.8 mL, 31.2 mmol, 2.5 equiv) is added and refluxing continued for 16 hrs. The mixture is allowed to stir at room temp. for 24 hrs before adding 5N NaOH (aq) sol. (8 mL). The mixture is refluxed for another hour, filtered and concentrated to yield 2.14 gr

of crude material containing the title compound. This material is used in the next steps without further purification due to poor stability of the product.

GC-MS m/z 149 (purity: 44%).

1-Methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazine-2-carboxylic acid tert-butyl ester

To a solution of 1-Methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine (69 g, 0.52 mol) in THF (600 ml) triethylamine (85 ml, 0.6 mol) and Boc_2O (130 ml) were added. The reaction mixture was stirred till the gas evolution completed (during 6 hours). The solvent was removed in vacuo, the residue was distilled in vacuo (bp=145-155 °C/12mm Hg) yielding the title compound (65 g, 52%).

LC/MS: m/z = 237 (MH^+)

6-Cyano-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazine-2-carboxylic acid tert-butyl ester

To a solution of 1-Methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazine-2-carboxylic acid tert-butyl ester (10 g, 0.042 mol) and triethylamine (35 ml, 0.25 mol) in toluene (100 ml) chlorosulfonyl isocyanate (4 ml, 0.045 mol) was added dropwise at 15°C. Then reaction mixture was refluxed for 6 hours. The toluene layer was washed with water (1 L), dried and the solvent was removed in vacuo. The residue was purified by chromatography on silica gel using hexane:ethylacetate 80:20 mixture as eluent yielding the title compound (4.5 g, 41%).

LC/MS: m/z = 262 (MH^+)

1-Methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carbonitrile

To a solution of 6-Cyano-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazine-2-carboxylic acid tert-butyl ester (4.5 g, 0.017 mol) in MeOH (100 ml) dioxane saturated with HCl (20 ml) was added. The reaction mixture was stirred for 5 min, then solvent was evaporated in vacuo and the residue treated with acetone resulting in 1.3 g (39%) of hydrochloride of the title compound.

LC/MS: m/z = 162 (MH^+)

1-Methyl-6-(2,2,2-trichloro-acetyl)-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazine-2-carboxylic acid tert-butyl ester

To a solution of 1-Methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazine-2-carboxylic acid tert-butyl ester (23.5 g, 0.1 mol) and triethylamine (20 ml, 0.14 mol) in CHCl_3 (250 ml) trichloroacetylchloride (12.7 ml) was added dropwise keeping the temperature of reaction mixture below 15°C. After 3-4 hours of stirring (reaction was monitored by ^{13}C NMR spectra) the reaction mixture was poured into saturated K_2CO_3 solution (0.5 L), organic layer was separated and dried over Na_2SO_4 . The solvent was removed in vacuo, the residue was treated with hexane yielding the title compound (34 g, 89%).

LC/MS: $m/z = 382$ (MH^+)

1-Methyl-6-methylcarbamoyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazine-2-carboxylic acid tert-butyl ester

The solution of 1-Methyl-6-(2,2,2-trichloro-acetyl)-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazine-2-carboxylic acid tert-butyl ester (15 g, 0.039 mol) in MeOH saturated with MeNH_2 (120 ml) was heated for 24 hours at 140°C in autoclave. Then the solvent was removed in vacuo and the residue was recrystallized from hexane yielding 6 g (53%) of the title compound.

LC/MS: $m/z = 294$ (MH^+)

1-Methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid methylamide

To a solution of 1-Methyl-6-methylcarbamoyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazine-2-carboxylic acid tert-butyl ester (5 g, 0.017 mol) in MeOH (100 ml) dioxane saturated with HCl (20 ml) was added. The reaction mixture was stirred for 5 min, then solvent was evaporated in vacuo and the residue treated with acetone. The resulted hydrochloride was dissolved in CHCl_3 (50 ml) and treated with saturated K_2CO_3 solution (50 ml). Organic layer was separated, dried over Na_2SO_4 ,

the solvent was removed in vacuo and the residue was re-crystallized from hexane resulting in 1.3 g (39%) of the title compound.

LC/MS: $m/z = 194$ (MH^+)

6-Cyclopropylcarbamoyl-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazine-2-carboxylic acid tert-butyl ester

The solution of 1-Methyl-6-(2,2,2-trichloro-acetyl)-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazine-2-carboxylic acid tert-butyl ester (15 g, 0.039 mol) and cyclopropylamine (11 g, 0.2 mol) in $CHCl_2$ was refluxed till compound 5 disappeared from reaction mixture (reaction was monitored by ^{13}C NMR spectra). Then the solvent was removed in vacuo and the residue was recrystallized from hexane yielding 5.5 g (44%) of the title compound.

LC/MS: $m/z = 320$ (MH^+)

1-Methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid cyclopropylamide

To a solution of 6-Cyclopropylcarbamoyl-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazine-2-carboxylic acid tert-butyl ester (5 g, 0.015 mol) in MeOH (100 ml) dioxane saturated with HCl (20 ml) was added. The reaction mixture was stirred for 5 min, then solvent was evaporated in vacuo and the residue treated with acetone. The resulted hydrochloride was dissolved in $CHCl_3$ (50 ml) and treated with saturated K_2CO_3 solution (50 ml). Organic layer was separated, dried over Na_2SO_4 , the solvent was removed in vacuo and the residue was re-crystallized from hexane resulting in 2.1 g (56%) of the title compound.

LC/MS: $m/z = 220$ (MH^+)

6-Ethylcarbamoyl-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazine-2-carboxylic acid tert-butyl ester

The solution of 1-Methyl-6-(2,2,2-trichloro-acetyl)-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazine-2-carboxylic acid tert-butyl ester (15 g, 0.039 mol) and ethylamine (9 g,

0.2 mol) in CHCl_2 was refluxed till compound 5 disappeared from reaction mixture (reaction was monitored by ^{13}C NMR spectra). Then the solvent was removed in vacuo and the residue was recrystallized from hexane yielding 5.8 g (48%) of the title compound.

LC/MS: $m/z = 308$ (MH^+)

1-Methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid ethylamide

To a solution of 6-Ethylcarbamoyl-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazine-2-carboxylic acid tert-butyl ester (5 g, 0.017 mol) in MeOH (100 ml) dioxane saturated with HCl (20 ml) was added. The reaction mixture was stirred for 5 min, then solvent was evaporated in vacuo and the residue treated with acetone. The resulted hydrochloride was dissolved in CHCl_3 (50 ml) and treated with saturated K_2CO_3 solution (50 ml). Organic layer was separated, dried over Na_2SO_4 , the solvent was removed in vacuo and the residue was re-crystallized from hexane resulting in 2.3 g (65%) of the title compound.

LC/MS: $m/z = 208$ (MH^+)

6-Isopropylcarbamoyl-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazine-2-carboxylic acid tert-butyl ester

The solution of 1-Methyl-6-(2,2,2-trichloro-acetyl)-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazine-2-carboxylic acid tert-butyl ester (15 g, 0.039 mol) and i-propylamine (11 g, 0.2 mol) in CHCl_2 was refluxed till compound 5 disappeared from reaction mixture (reaction was monitored by ^{13}C NMR spectra). Then the solvent was removed in vacuo and the residue was recrystallized from hexane yielding 5.5 g (43%) of the title compound.

LC/MS: $m/z = 322$ (MH^+)

1-Methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid isopropylamide

To a solution of 6-Isopropylcarbamoyl-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazine-2-carboxylic acid tert-butyl ester (5 g, 0.015 mol) in MeOH (100 ml) dioxane saturated with HCl (20 ml) was added. The reaction mixture was stirred for 5 min, then solvent was evaporated in vacuo and the residue treated with acetone. The resulted hydrochloride was dissolved in CHCl_3 (50 ml) and treated with saturated K_2CO_3 solution (50 ml). Organic layer was separated, dried over Na_2SO_4 , the solvent was removed in vacuo and the residue was re-crystallized from hexane resulting in 1.5 g (45%) of the title compound.

LC/MS: $m/z = 222$ (MH^+)

(2,4-Difluorophenyl)(oxo)acetaldehyde

SeO_2 (35.6 g, 0.32 mol, 1 equiv) was added to a solution of 2,4-difluoroacetophenone (50 g, 0.32 mol, 1 equiv) in a mixture dioxane- H_2O (175 ml : 7 ml, respectively) and the mixture was refluxed for 5 hrs. The reaction mixture was evaporated. Distillation yielded (b.p 130-135 C/1 mm Hg) 30 g (55%) of the title compound.

LC/MS: $m/z = 171$ (MH^+)

(2,4-Difluorophenyl)(oxo)acetaldehyde methylhydrazone

Methyl hydrazine (18.5 g, 0.4 mol, 2.3 equiv) was dropwise added to a solution of (2,4-difluorophenyl)(oxo)acetaldehyde (30 g, 0.176 mol, 1.0 equiv) in $\text{MeOH}:\text{H}_2\text{O}:\text{HOAc}$ (300 ml: 300 ml: 50 ml) and the mixture was stirred at room temperature for 24 hrs. The precipitate was filtered off and washed with water to yield 18 g (51.5%) of the title compound.

LC/MS: $m/z = 199$ (MH^+)

7-Fluorocinnolin-4(1H)-one

K_2CO_3 (21.2 g, 0.1534 mol, 2 equiv) was added to a solution of (2,4-difluorophenyl)(oxo)acetaldehyde methylhydrazone (15.2 g, 0.0767 mol, 1.0 equiv) in DMF (30 ml) and the mixture was stirred at 100-105 C for 8 hrs. The reaction

mixture was diluted with water. The precipitate was filtered off and washed with water to yield 6.2 g (45.5%) of the title compound.

LC/MS: $m/z = 179$ (MH^+)

7-Fluoro-1-methyl-1,2,3,4-tetrahydro-cinnoline dihydrochloride

A solution of 7-fluorocinnolin-4(1H)-one (7.3 g, 0.0225 mol, 1 equiv) in benzene (100 ml) was treated with $LiAlH_4$ (6.08 g, 0.16 mol, 4 equiv) in Et_2O (100 ml) and refluxed for 5 hrs. The mixture was allowed to stir at room temp. for 24 hrs before adding NaOH (5 g) in H_2O (15 ml). The mixture was refluxed for 1 hour, filtered and concentrated. Distillation yielded 7-fluoro-1-methyl-1,2,3,4-tetrahydro-cinnoline (b.p 150-155 C/1 mm). Amine was dissolved in MeOH (30 ml) and HCl was bubbled (10 min), methanol was evaporated and residue was treated with Et_2O to yielded 2.55 g (32%) of title compound.

LC/MS: $m/z = 167$ (MH^+)

2-Azido-ethanol

To a solution of NaN_3 (157 g, 3 mol) in H_2O (500 ml) 2-chloro-ethanol (161 g, 0.2 mol) was added and reaction mixture was stirred at 70°C for 60 hours. Then it was saturated with Na_2SO_4 , extracted with CH_2Cl_2 , organic layer was separated and dried over Na_2SO_4 . The solvent was removed in vacuo affording the title compound as a colorless liquid (156.6 g, 90%).

LC/MS: $m/z = 88$ (MH^+)

Toluene-4-sulfonic acid 2-azido-ethyl ester

To a solution of 2-Azido-ethanol (100 g, 1.15 mol) in CH_2Cl_2 (600 ml) a solution of TosCl (220 g, 1.15 mol) in CH_2Cl_2 (400ml) was added dropwise keeping temperature at 0°C. Then the reaction mixture was stirred for 4 hours, washed with water (4x300 ml) and the organic layer was dried over Na_2SO_4 . The solvent was removed in vacuo affording the title compound as a pale-yellow oil (235.6 g, 85%).

LC/MS: $m/z = 242$ (MH^+)

(2-Azido-ethyl)-benzyl-amine

A solution of benzylamine (95 ml, 1 mol) and Toluene-4-sulfonic acid 2-azido-ethyl ester (100 g, 0.41 mol) in CH₃CN (400ml) was refluxed with stirring for 7 hours, then the precipitate was filtered off and the solvent was removed in vacuo. The crude residue was subjected to column chromatography over SiO₂ using hexane as eluent affording the title compound as a pale-yellow liquid (55 g, 75%).

LC/MS: m/z = 177 (MH⁺)

[(2-Azido-ethyl)-benzyl-amino]-acetic acid ethyl ester

To a solution of (2-Azido-ethyl)-benzyl-amine (20 g, 0.11 mol), bromo-acetic acid ethyl ester (23 g, 0.13 mol) in EtOH (150 ml) K₂CO₃ (25 g, 0.18 mol) and Trident ((N(CH₂CH₂OCH₂CH₂OMe)₃, 3.7 g, 0.011 mol) were added. The reaction mixture was refluxed for 3 hours, cooled, poured into water and extracted with CCl₄. The organic layer was washed with water, dried over Na₂SO₄, the solvent was removed in vacuo yielding the title compound as a colorless oil (23 g, 77%).

LC/MS: m/z = 263 (MH⁺)

1-Benzyl-5-ethoxy-1,2,3,6-tetrahydro-pyrazine

Triphenylphosphine (21 g, 0.8 mol) was added to a solution of [(2-Azido-ethyl)-benzyl-amino]-acetic acid ethyl ester (21 g, 0.8 mol) in toluene under Ar atmosphere, then the reaction mixture was stirred at reflux for 8 hours and the solvent was removed in vacuo. The product was extracted from the residue with hot hexane. The solvent was evaporated and the crude product was subjected to flash column chromatography over SiO₂ using hexane as eluent affording mixture of the title compound with by-product - 4-benzyl-1-ethyl-piperazin-2-one in 3:1 ratio (10 g). This mixture was used in the next step without additional purification.

LC/MS: m/z = 219 (MH⁺)

7-Benzyl-3-methyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine dihydrochloride

To the mixture of 1-Benzyl-5-ethoxy-1,2,3,6-tetrahydro-pyrazine and 4-benzyl-1-ethyl-piperazin-2-one (4 g) dissolved in toluene (20 ml) prop-2-ynylamine (0.8 g, 0.014 mol) was added and the reaction mixture was refluxed for 8-9 hours. Then the solvent was removed in vacuo and the product was extracted from the residue with hot hexane. The solvent was evaporated and the crude product obtained was subjected to flash column chromatography over SiO₂ using hexane as eluent. The residue was dissolved in minimal amount of Et₂O (~ 30 mL) and dry HCl was bubbled at -5 °C through the solution obtained. The precipitate formed was filtered off and re-crystallized from MeCN affording the title compound as its dihydrochloride salt (2.35 g, 60%).

LC/MS: m/z = 228 (MH⁺)

3-Methyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine dihydrochloride

To a solution of 7-Benzyl-3-methyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine dihydrochloride (2.9 g, 0.012 mol) in MeOH (100 ml) Pd/C (200 mg) was added and the reaction mixture was kept at 60°C in autoclave for 5 hours (at 50 atm) and then stirred for 14 hours at RT. The precipitate was filtered off, and the solvent was removed in vacuo yielding the title compound (1.51 g, 74%).

LC/MS: m/z = 138 (MH⁺)

The following compounds according to the invention are prepared as examples, which are intended as an illustration of and not a limitation upon the scope of the invention:

Example 1

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

A solution of 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (181 mg, 0.92 mmol, 1.0 equiv), 1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine (150 mg, 1.10 mmol, 1.2 equiv), EDC (176 mg, 0.92 mmol, 1.0 equiv) and HOBt (125 mg, 0.92

mmol, 1.0 equiv) in DMF (5 mL) was heated at 50°C for 4 h. The mixture was allowed to cool to room temperature and poured into water and extracted with ethyl acetate. The combined organic layers were washed three times with brine, dried over Na₂SO₄ and concentrated. The residue was subjected to flash column chromatography (40% ethyl acetate in heptane) to yield 265 mg (91%) of the title compound in good to moderate yield.

LC/MS: m/z = 317 (MH⁺)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 2

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,2,3,4-Tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: m/z = 303 (MH⁺)

Example 3

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: m/z = 359, 361 (MH⁺)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 4

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,2,3,4-Tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 345, 347$ (MH^+)

Example 5

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6-dimethyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,6-Dimethyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 330$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 6

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 316$ (MH^+)

Example 7

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6-dimethyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,6-Dimethyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 373, 375$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 8

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 359, 361$ (MH^+)

Example 9

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(4-methyl-6,7-dihydro-4H-[1,2,3]triazolo[1,5-a]pyrazin-5-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 4-Methyl-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 318$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 10

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dihydro-4H-[1,2,3]triazolo[1,5-a]pyrazin-5-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 4,5,6,7-Tetrahydro-[1,2,3]triazolo[1,5-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 304$ (MH^+)

Example 11

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(4-methyl-6,7-dihydro-4H-[1,2,3]triazolo[1,5-a]pyrazin-5-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 4-Methyl-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 361, 363$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 12

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dihydro-4H-[1,2,3]triazolo[1,5-a]pyrazin-5-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 4,5,6,7-Tetrahydro-[1,2,3]triazolo[1,5-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 347, 349$ (MH^+)

Example 13

7-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-8-methyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine-2-carboxylic acid ethyl ester

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-Methyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine-2-carboxylic acid ethyl ester to provide the title compound in good to moderate yield.

LC/MS: $m/z = 389$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 14

7-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine-2-carboxylic acid ethyl ester

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 5,6,7,8-Tetrahydro-imidazo[1,2-a]pyrazine-2-carboxylic acid ethyl ester to provide the title compound in good to moderate yield.

LC/MS: $m/z = 375$ (MH^+)

Example 15

7-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-8-methyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine-2-carboxylic acid ethyl ester

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-Methyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine-2-carboxylic acid ethyl ester to provide the title compound in good to moderate yield.

LC/MS: $m/z = 432, 434$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 16

7-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine-2-carboxylic acid ethyl ester

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 5,6,7,8-Tetrahydro-imidazo[1,2-a]pyrazine-2-carboxylic acid ethyl ester to provide the title compound in good to moderate yield.

LC/MS: $m/z = 418, 420$ (MH^+)

Example 17

7-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-8-methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine-3-carboxylic acid ethyl ester

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-Methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine-3-carboxylic acid ethyl ester to provide the title compound in good to moderate yield.

LC/MS: $m/z = 390$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 18

7-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine-3-carboxylic acid ethyl ester

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 5,6,7,8-Tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine-3-carboxylic acid ethyl ester to provide the title compound in good to moderate yield.

LC/MS: $m/z = 376$ (MH^+)

Example 19

7-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-8-methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine-3-carboxylic acid ethyl ester

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-Methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine-3-carboxylic acid ethyl ester to provide the title compound in good to moderate yield.

LC/MS: $m/z = 433, 435$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 20

7-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine-3-carboxylic acid ethyl ester

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 5,6,7,8-Tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine-3-carboxylic acid ethyl ester to provide the title compound in good to moderate yield.

LC/MS: $m/z = 419, 421$ (MH^+)

Example 21

(3-Bromo-8-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-Bromo-8-methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 397$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 22

(3-Bromo-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-Bromo-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 383$ (MH^+)

Example 23

(3-Bromo-8-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-Bromo-8-methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 440, 442$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 24

(3-Bromo-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-Bromo-5,6,7,8-tetrahydro-

[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 426, 428$ (MH^+)

Example 25

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-Methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 318$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 26

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 5,6,7,8-Tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 304$ (MH^+)

Example 27

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-Methyl-5,6,7,8-tetrahydro-

[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 361, 363$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 28

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 5,6,7,8-Tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 347, 349$ (MH^+)

Example 29

(6-Chloro-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Chloro-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

LC/MS: $m/z = 350$ (MH^+)

Example 30

(6-Chloro-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Chloro-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 336$ (MH^+)

Example 31

(6-Chloro-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Chloro-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 394, 396$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 32

(6-Chloro-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Chloro-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 380, 382$ (MH^+)

Example 33

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dibromo-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6,7-Dibromo-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 473$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 34

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dibromo-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6,7-Dibromo-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 459$ (MH^+)

Example 35

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dibromo-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6,7-Dibromo-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 517, 519$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 36

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dibromo-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6,7-Dibromo-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 506$ (MH^+)

Example 37

(6-Bromo-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Bromo-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 395$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 38

(6-Bromo-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Bromo-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 381$ (MH^+)

Example 39

(6-Bromo-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Bromo-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 440$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 40

(6-Bromo-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Bromo-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 426$ (MH^+)

Example 41

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-5-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 4-Methyl-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 317$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 42

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-5-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 4,5,6,7-Tetrahydro-pyrazolo[1,5-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 303$ (MH^+)

Example 43

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(4-methyl-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-5-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 4-Methyl-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 360, 362$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 44

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-5-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 4,5,6,7-Tetrahydro-pyrazolo[1,5-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 346, 348$ (MH^+)

Example 45

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-Methyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 317$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 46

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 5,6,7,8-Tetrahydro-imidazo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 303$ (MH^+)

Example 47

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-Methyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 360, 362$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 48

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 5,6,7,8-Tetrahydro-imidazo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 346, 348$ (MH^+)

Example 49

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(2,8-dimethyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 2,8-Dimethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 331$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 50

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(2-methyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 2-Methyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 317$ (MH^+)

Example 51

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(2,8-dimethyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 2,8-Dimethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 374, 376$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 52

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(2-methyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 2-Methyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 360, 362$ (MH^+)

Example 53

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3,8-dimethyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3,8-Dimethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 331$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 54

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-methyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-Methyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 317$ (MH^+)

Example 55

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3,8-dimethyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3,8-Dimethyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 374, 376$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 56

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-methyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-Methyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 360, 362$ (MH^+)

Example 57

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3,8-dimethyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3,8-Dimethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 332$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 58

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-Methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 318$ (MH^+)

Example 59

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3,8-dimethyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3,8-Dimethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 375, 377$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 60

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-Methyl-5,6,7,8-tetrahydro-

[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 361, 363$ (MH^+)

Example 61

2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carbonitrile

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carbonitrile to provide the title compound in good to moderate yield.

LC/MS: $m/z = 340$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 62

2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carbonitrile

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,2,3,4-Tetrahydro-pyrrolo[1,2-a]pyrazine-6-carbonitrile to provide the title compound in good to moderate yield.

LC/MS: $m/z = 327$ (MH^+)

Example 63

2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carbonitrile

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-1,2,3,4-tetrahydro-

pyrrolo[1,2-a]pyrazine-6-carbonitrile to provide the title compound in good to moderate yield.

LC/MS: $m/z = 384, 386$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 64

2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carbonitrile

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,2,3,4-Tetrahydro-pyrrolo[1,2-a]pyrazine-6-carbonitrile to provide the title compound in good to moderate yield.

LC/MS: $m/z = 370, 372$ (MH^+)

Example 65

2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid methylamide

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid methylamide to provide the title compound in good to moderate yield.

LC/MS: $m/z = 373$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 66

2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid methylamide

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,2,3,4-Tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid methylamide to provide the title compound in good to moderate yield.

LC/MS: $m/z = 359$ (MH^+)

Example 67

2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid methylamide

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid methylamide to provide the title compound in good to moderate yield.

LC/MS: $m/z = 416, 418$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 68

2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid methylamide

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,2,3,4-Tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid methylamide to provide the title compound in good to moderate yield.

LC/MS: $m/z = 402, 404$ (MH^+)

Example 69

2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid cyclopropylamide

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid cyclopropylamide to provide the title compound in good to moderate yield.

LC/MS: $m/z = 399$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 70

2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid cyclopropylamide

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,2,3,4-Tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid cyclopropylamide to provide the title compound in good to moderate yield.

LC/MS: $m/z = 385$ (MH^+)

Example 71

2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid cyclopropylamide

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid cyclopropylamide to provide the title compound in good to moderate yield.

LC/MS: $m/z = 442, 444$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 72

2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid cyclopropylamide

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,2,3,4-Tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid cyclopropylamide to provide the title compound in good to moderate yield.

LC/MS: $m/z = 428, 430$ (MH^+)

Example 73

2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid ethylamide

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid ethylamide to provide the title compound in good to moderate yield.

LC/MS: $m/z = 387$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 74

2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid ethylamide

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,2,3,4-Tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid ethylamide to provide the title compound in good to moderate yield.

LC/MS: $m/z = 373$ (MH^+)

Example 75

2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid ethylamide

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid ethylamide to provide the title compound in good to moderate yield.

LC/MS: $m/z = 430, 432$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 76

2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid ethylamide

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,2,3,4-Tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid ethylamide to provide the title compound in good to moderate yield.

LC/MS: $m/z = 416, 418$ (MH^+)

Example 77

2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid isopropylamide

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid isopropylamide to provide the title compound in good to moderate yield.

LC/MS: $m/z = 401$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 78

2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid isopropylamide

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid isopropylamide to provide the title compound in good to moderate yield.

LC/MS: $m/z = 387$ (MH^+)

Example 79

2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid isopropylamide

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid isopropylamide to provide the title compound in good to moderate yield.

LC/MS: $m/z = 444, 446$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 80

2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid isopropylamide

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,2,3,4-tetrahydro-pyrrolo[1,2-

a]pyrazine-6-carboxylic acid isopropylamide to provide the title compound in good to moderate yield.

LC/MS: $m/z = 430, 432$ (MH^+)

Example 81

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-6-(1H-tetrazol-5-yl)-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-6-(1H-tetrazol-5-yl)-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 384$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 82

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[6-(1H-tetrazol-5-yl)-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-(1H-Tetrazol-5-yl)-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 370$ (MH^+)

Example 83

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-6-(1H-tetrazol-5-yl)-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-6-(1H-tetrazol-5-yl)-

1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 427, 429$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 84

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[6-(1H-tetrazol-5-yl)-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-(1H-Tetrazol-5-yl)-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 413, 415$ (MH^+)

Example 85

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyridin-2-yl)-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-6-pyridin-2-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 393$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 86

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyridin-2-yl)-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Pyridin-2-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 379$ (MH^+)

Example 87

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyridin-2-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-6-pyridin-2-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 436, 438$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 88

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyridin-2-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Pyridin-2-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 422, 424$ (MH^+)

Example 89

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyridin-3-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-6-pyridin-3-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 393$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 90

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyridin-3-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Pyridin-3-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 379$ (MH^+)

Example 91

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyridin-3-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-6-pyridin-3-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 436, 438$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 92

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyridin-3-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Pyridin-3-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 422, 424$ (MH^+)

Example 93

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyridin-4-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-6-pyridin-4-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 393$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 94

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyridin-4-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Pyridin-3-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 379$ (MH^+)

Example 95

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyridin-4-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-6-pyridin-4-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 436, 438$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 96

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyridin-4-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Pyridin-4-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 422, 424$ (MH^+)

Example 97

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-thiophen-2-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-6-thiophen-2-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 398$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 98

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-thiophen-2-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Thiophen-2-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 384$ (MH^+)

Example 99

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-thiophen-2-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-6-thiophen-2-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 441, 443$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 100

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-thiophen-2-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Thiophen-2-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 427, 429$ (MH^+)

Example 101

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-furan-2-yl-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Furan-2-yl-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 384$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 102

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-furan-2-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Furan-2-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 368$ (MH^+)

Example 103

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-furan-2-yl-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Furan-2-yl-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 425, 427$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 104

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-furan-2-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Furan-2-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 411, 413$ (MH^+)

Example 105

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-thiophen-3-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-6-thiophen-3-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 398$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 106

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-thiophen-3-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Thiophen-3-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 384$ (MH^+)

Example 107

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-thiophen-3-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-6-thiophen-3-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 441, 443$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 108

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-thiophen-3-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Thiophen-3-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 427, 429$ (MH^+)

Example 109

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-furan-3-yl-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Furan-3-yl-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 383$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 110

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-furan-3-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Furan-3-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 368$ (MH^+)

Example 111

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-furan-3-yl-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Furan-3-yl-1-methyl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 425, 427$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 112

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-furan-3-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Furan-3-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 411, 413$ (MH^+)

Example 113

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyrimidin-4-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-6-pyrimidin-4-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 394$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 114

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyrimidin-4-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Pyrimidin-4-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 380$ (MH^+)

Example 115

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyrimidin-4-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-6-pyrimidin-4-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 437, 439$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 116

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyrimidin-4-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Pyrimidin-4-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 423, 425$ (MH^+)

Example 117

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyrimidin-5-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-6-pyrimidin-5-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 394$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 118

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyrimidin-5-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Pyrimidin-5-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 380$ (MH^+)

Example 119

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyrimidin-5-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-6-pyrimidin-5-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 437, 439$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 120

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyrimidin-5-yl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Pyrimidin-5-yl-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 423, 425$ (MH^+)

Example 121

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-3-pyridin-2-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-Methyl-3-pyridin-2-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 395$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 122

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-pyridin-2-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-Pyridin-2-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 381$ (MH^+)

Example 123

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-3-pyridin-2-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-Methyl-3-pyridin-2-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 438, 440$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 124

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-pyridin-2-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-Pyridin-2-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 424, 426$ (MH^+)

Example 125

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-3-pyridin-3-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-Methyl-3-pyridin-3-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 395$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 126

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-pyridin-3-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-Pyridin-3-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 381$ (MH^+)

Example 127

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-3-pyridin-3-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-methyl-3-pyridin-3-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 438, 440$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 128

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-pyridin-3-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-pyridin-3-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 424, 426$ (MH^+)

Example 129

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-3-pyridin-4-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-methyl-3-pyridin-4-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 395$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 130

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-pyridin-4-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-pyridin-4-yl-5,6,7,8-tetrahydro-

[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 381$ (MH^+)

Example 131

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-3-pyridin-4-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-methyl-3-pyridin-4-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 438, 440$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 132

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-pyridin-4-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-pyridin-4-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 424, 426$ (MH^+)

Example 133

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-3-thiophen-2-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-methyl-3-thiophen-2-yl-5,6,7,8-

tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 400$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 134

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-thiophen-2-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-thiophen-2-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 386$ (MH^+)

Example 135

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-3-thiophen-2-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-methyl-3-thiophen-2-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 443, 445$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 136

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-thiophen-2-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-thiophen-2-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 429, 431$ (MH^+)

Example 137

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-furan-2-yl-8-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-Furan-2-yl-8-methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 384$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 138

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-furan-2-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-Furan-2-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 370$ (MH^+)

Example 139

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-furan-2-yl-8-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-Furan-2-yl-8-methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 427, 429$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 140

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-furan-2-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-Furan-2-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 413, 415$ (MH^+)

Example 141

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-3-thiophen-3-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-methyl-3-thiophen-3-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 400$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 142

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-thiophen-3-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-thiophen-3-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 386$ (MH^+)

Example 143

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-3-thiophen-3-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-methyl-3-thiophen-3-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 443, 445$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 144

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-thiophen-3-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-thiophen-3-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 429, 431$ (MH^+)

Example 145

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-furan-3-yl-8-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-furan-3-yl-8-methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 384$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 146

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-furan-3-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-furan-3-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 370$ (MH^+)

Example 147

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-furan-3-yl-8-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-furan-3-yl-8-methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 427, 429$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 148

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-furan-3-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-furan-3-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 413, 415$ (MH^+)

Example 149

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-3-pyrimidin-4-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-methyl-3-pyrimidin-4-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 396$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 150

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-pyrimidin-4-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-pyrimidin-4-yl-5,6,7,8-tetrahydro-

[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 382$ (MH^+)

Example 151

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-3-pyrimidin-4-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-Methyl-3-pyrimidin-4-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 439, 441$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 152

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-pyrimidin-4-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-Pyrimidin-4-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 425, 427$ (MH^+)

Example 153

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-3-pyrimidin-5-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-Methyl-3-pyrimidin-5-yl-5,6,7,8-

tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 396$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 154

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-pyrimidin-5-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-Pyrimidin-5-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 382$ (MH^+)

Example 155

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-3-pyrimidin-5-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-Methyl-3-pyrimidin-5-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 439, 441$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 156

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-pyrimidin-5-yl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-Pyrimidin-5-yl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 425, 427 (MH^+)$

Example 157

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(6-fluoro-pyridin-3-yl)-8-methyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-(6-Fluoro-pyridin-3-yl)-8-methyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 412 (MH^+)$

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 158

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(6-fluoro-pyridin-3-yl)-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-(6-Fluoro-pyridin-3-yl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 398 (MH^+)$

Example 159

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(6-fluoro-pyridin-3-yl)-8-methyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-(6-Fluoro-pyridin-3-yl)-8-methyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 455, 457$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 160

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(6-fluoro-pyridin-3-yl)-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-(6-Fluoro-pyridin-3-yl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 441, 443$ (MH^+)

Example 161

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(2-fluoro-pyridin-3-yl)-8-methyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-(2-Fluoro-pyridin-3-yl)-8-methyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 412$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 162

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(2-fluoro-pyridin-3-yl)-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-(2-Fluoro-pyridin-3-yl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 398$ (MH^+)

Example 163

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(2-fluoro-pyridin-3-yl)-8-methyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-(2-Fluoro-pyridin-3-yl)-8-methyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 455, 457$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 164

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(2-fluoro-pyridin-3-yl)-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-(2-Fluoro-pyridin-3-yl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 441, 443$ (MH^+)

Example 165

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[2-(6-fluoro-pyridin-3-yl)-8-methyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 2-(6-Fluoro-pyridin-3-yl)-8-methyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 411$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 166

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[2-(6-fluoro-pyridin-3-yl)-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 2-(6-Fluoro-pyridin-3-yl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 398$ (MH^+)

Example 167

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[2-(6-fluoro-pyridin-3-yl)-8-methyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 2-(6-Fluoro-pyridin-3-yl)-8-methyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 455, 457$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 168

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[2-(6-fluoro-pyridin-3-yl)-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 2-(6-Fluoro-pyridin-3-yl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 441, 443$ (MH^+)

Example 169

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[2-(2-fluoro-pyridin-3-yl)-8-methyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 2-(2-Fluoro-pyridin-3-yl)-8-methyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 411$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 170

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[2-(2-fluoro-pyridin-3-yl)-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 2-(2-Fluoro-pyridin-3-yl)-5,6,7,8-

tetrahydro-imidazo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 397$ (MH^+)

Example 171

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[2-(2-fluoro-pyridin-3-yl)-8-methyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 2-(2-Fluoro-pyridin-3-yl)-8-methyl-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 455, 457$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 172

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[2-(2-fluoro-pyridin-3-yl)-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 2-(2-Fluoro-pyridin-3-yl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 441, 443$ (MH^+)

Example 173

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(6-fluoro-pyridin-3-yl)-8-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-(6-Fluoro-pyridin-3-yl)-8-methyl-

5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 412$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 174

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(6-fluoro-pyridin-3-yl)-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-(6-Fluoro-pyridin-3-yl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 398$ (MH^+)

Example 175

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(6-fluoro-pyridin-3-yl)-8-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-(6-Fluoro-pyridin-3-yl)-8-methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 456, 458$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 176

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(6-fluoro-pyridin-3-yl)-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-(6-Fluoro-pyridin-3-yl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 442, 444$ (MH^+)

Example 177

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(2-fluoro-pyridin-3-yl)-8-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-(2-Fluoro-pyridin-3-yl)-8-methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 413$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 178

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(2-fluoro-pyridin-3-yl)-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-methanone

In close analogy to the procedure described in Example 1, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-(2-Fluoro-pyridin-3-yl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 399$ (MH^+)

Example 179

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(2-fluoro-pyridin-3-yl)-8-methyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-(2-Fluoro-pyridin-3-yl)-8-methyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 456, 458$ (MH^+)

The stereo-isomers of this compound are separated. The S-configured compound has a different activity than the R-configured compound.

Example 180

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[3-(2-fluoro-pyridin-3-yl)-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-methanone

In close analogy to the procedure described in Example 1, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 3-(2-Fluoro-pyridin-3-yl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 442, 444$ (MH^+)

Example 181

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

Oxalyl chloride (430 μ L, 5.0 mmol, 5.0 equiv) was added to a stirred suspension of 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (197 mg, 1.0 mmol, 1.0 equiv) in DCM (5 mL), followed by the addition of a few drops of DMF. The mixture was stirred for 16 hrs and concentrated to dryness. The residue was co-evaporated with toluene and DCM. The residue was dissolved in DCM (5 mL) and treated with TEA (287 μ L, 2.06 mmol, 2.5 equiv) and 1-methyl-1,2,3,4-tetrahydro-cinnoline (504 mg [purity:44%] $\approx$ 1.5 mmol, 1.5 equiv). After stirring for 16 hrs, the reaction mixture was quenched with water and the aqueous layer was extracted with DCM. The combined organic layers were dried over Na_2SO_4 , concentrated and

purified by flash column chromatography (25% to 75% EtOAc in heptane) to give 221 mg of material containing the title compound. Further purification by preparative LC-MS afforded 124 mg (37%) of the title compound.

LC/MS: $m/z = 328$ (MH^+)

Example 182

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 371, 373$ (MH^+)

Example 183

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-thieno[3,2-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-1,2,3,4-tetrahydro-thieno[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 334$ (MH^+)

Example 184

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-thieno[3,2-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-1,2,3,4-tetrahydro-thieno[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 377, 379$ (MH^+)

Example 185

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6-dimethyl-3,4-dihydro-1H-thieno[3,2-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,6-Dimethyl-1,2,3,4-tetrahydro-thieno[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 348$ (MH^+)

Example 186

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6-dimethyl-3,4-dihydro-1H-thieno[3,2-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,6-Dimethyl-1,2,3,4-tetrahydro-thieno[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 391, 393$ (MH^+)

Example 187

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,7-dimethyl-3,4-dihydro-1H-thieno[3,2-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,7-Dimethyl-1,2,3,4-tetrahydro-thieno[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 348$ (MH^+)

Example 188

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,7-dimethyl-3,4-dihydro-1H-thieno[3,2-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,7-Dimethyl-1,2,3,4-tetrahydro-thieno[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 391, 393$ (MH^+)

Example 189

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6,7-trimethyl-3,4-dihydro-1H-thieno[3,2-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,6,7-Trimethyl-1,2,3,4-tetrahydro-thieno[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 362$ (MH^+)

Example 190

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6,7-trimethyl-3,4-dihydro-1H-thieno[3,2-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,6,7-Trimethyl-1,2,3,4-tetrahydro-thieno[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 405, 407$ (MH^+)

Example 191

(6-Bromo-1-methyl-3,4-dihydro-1H-thieno[3,2-c]pyridazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Bromo-1-methyl-1,2,3,4-tetrahydro-thieno[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 413$ (MH^+)

Example 192

(6-Bromo-1-methyl-3,4-dihydro-1H-thieno[3,2-c]pyridazin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Bromo-1-methyl-1,2,3,4-tetrahydro-thieno[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 456, 458$ (MH^+)

Example 193

(6-Chloro-1-methyl-3,4-dihydro-1H-thieno[3,2-c]pyridazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Chloro-1-methyl-1,2,3,4-tetrahydro-thieno[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 369$ (MH^+)

Example 194

(6-Bromo-1-methyl-3,4-dihydro-1H-thieno[3,2-c]pyridazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Chloro-1-methyl-1,2,3,4-tetrahydro-thieno[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 413$ (MH^+)

Example 195

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-furo[3,2-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-1,2,3,4-tetrahydro-furo[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 318$ (MH^+)

Example 196

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-furo[3,2-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-1,2,3,4-tetrahydro-furo[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 361, 363$ (MH^+)

Example 197

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6-dimethyl-3,4-dihydro-1H-furo[3,2-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,6-Dimethyl-1,2,3,4-tetrahydro-furo[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 332$ (MH^+)

Example 198

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6-dimethyl-3,4-dihydro-1H-furo[3,2-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,6-Dimethyl-1,2,3,4-tetrahydro-furo[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 375, 377$ (MH^+)

Example 199

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,7-dimethyl-3,4-dihydro-1H-furo[3,2-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,7-Dimethyl-1,2,3,4-tetrahydro-furo[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 332$ (MH^+)

Example 200

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,7-dimethyl-3,4-dihydro-1H-furo[3,2-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,7-Dimethyl-1,2,3,4-tetrahydro-furo[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 375, 377$ (MH^+)

Example 201

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6,7-trimethyl-3,4-dihydro-1H-furo[3,2-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,6,7-Trimethyl-1,2,3,4-tetrahydro-furo[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 346$ (MH^+)

Example 202

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6,7-trimethyl-3,4-dihydro-1H-furo[3,2-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,6,7-Trimethyl-1,2,3,4-tetrahydro-furo[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 389, 391$ (MH^+)

Example 203

(6-Bromo-1-methyl-3,4-dihydro-1H-furo[3,2-c]pyridazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Bromo-1-methyl-1,2,3,4-tetrahydro-furo[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 396$ (MH^+)

Example 204

(6-Bromo-1-methyl-3,4-dihydro-1H-furo[3,2-c]pyridazin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Bromo-1-methyl-1,2,3,4-tetrahydro-furo[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 443$ (MH^+)

Example 205

(6-Chloro-1-methyl-3,4-dihydro-1H-furo[3,2-c]pyridazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Chloro-1-methyl-1,2,3,4-tetrahydro-furo[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 352$ (MH^+)

Example 206

(6-Bromo-1-methyl-3,4-dihydro-1H-furo[3,2-c]pyridazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Chloro-1-methyl-1,2,3,4-tetrahydro-furo[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 398$ (MH^+)

Example 207

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-1,3,4,5-tetrahydro-pyrrolo[3,2-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 317$ (MH^+)

Example 208

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-1,3,4,5-tetrahydro-pyrrolo[3,2-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 360, 362$ (MH^+)

Example 209

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6-dimethyl-1,3,4,5-tetrahydro-pyrrolo[3,2-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,6-Dimethyl-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 331$ (MH^+)

Example 210

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6-dimethyl-1,3,4,5-tetrahydro-pyrrolo[3,2-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,6-Dimethyl-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 374, 376$ (MH^+)

Example 211

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,7-dimethyl-1,3,4,5-tetrahydro-pyrrolo[3,2-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,7-Dimethyl-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 331$ (MH^+)

Example 212

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,7-dimethyl-1,3,4,5-tetrahydro-pyrrolo[3,2-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,7-Dimethyl-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 374, 376$ (MH^+)

Example 213

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6,7-trimethyl-1,3,4,5-tetrahydro-pyrrolo[3,2-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,6,7-Trimethyl-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 345$ (MH^+)

Example 214

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6,7-trimethyl-1,3,4,5-tetrahydro-pyrrolo[3,2-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,6,7-Trimethyl-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 388, 390$ (MH^+)

Example 215

(6-Bromo-1-methyl-1,3,4,5-tetrahydro-pyrrolo[3,2-c]pyridazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Bromo-1-methyl-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 397$ (MH^+)

Example 216

(6-Bromo-1-methyl-1,3,4,5-tetrahydro-pyrrolo[3,2-c]pyridazin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Bromo-1-methyl-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 442$ (MH^+)

Example 217

(6-Chloro-1-methyl-1,3,4,5-tetrahydro-pyrrolo[3,2-c]pyridazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 352$ (MH^+)

Example 218

(6-Bromo-1-methyl-1,3,4,5-tetrahydro-pyrrolo[3,2-c]pyridazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-pyrrolo[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 397$ (MH^+)

Example 219

(8-Chloro-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-Chloro-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 362$ (MH^+)

Example 220

(8-Bromo-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-Chloro-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 408$ (MH^+)

Example 221

(7-Chloro-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 7-Chloro-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 362$ (MH^+)

Example 222

(7-Bromo-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 7-Chloro-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 408$ (MH^+)

Example 223

(6-Chloro-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Chloro-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 362$ (MH^+)

Example 224

(6-Bromo-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Chloro-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 408$ (MH^+)

Example 225

(5-Chloro-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 5-Chloro-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 362$ (MH^+)

Example 226

(5-Bromo-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 5-Chloro-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 408$ (MH^+)

Example 227

(8-Bromo-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-Bromo-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 408$ (MH^+)

Example 228

(8-Bromo-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-Bromo-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 453$ (MH^+)

Example 229

(7-Bromo-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 7-Bromo-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 408$ (MH^+)

Example 230

(7-Bromo-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 7-Bromo-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 453$ (MH^+)

Example 231

(6-Bromo-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Bromo-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 408$ (MH^+)

Example 232

(6-Bromo-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Bromo-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 453$ (MH^+)

Example 233

(5-Bromo-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 5-Bromo-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 408$ (MH^+)

Example 234

(5-Bromo-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 5-Bromo-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 453$ (MH^+)

Example 235

(8-Fluoro-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-Fluoro-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 346$ (MH^+)

Example 236

(8-Fluoro-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-Fluoro-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 389, 391$ (MH^+)

Example 237

(7-Fluoro-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 7-Fluoro-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 346$ (MH^+)

Example 238

(7-Fluoro-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 7-Fluoro-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 389, 391$ (MH^+)

Example 239

(6-Fluoro-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Fluoro-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 346$ (MH^+)

Example 240

(6-Fluoro-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Fluoro-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 389, 391$ (MH^+)

Example 241

(5-Fluoro-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 5-Fluoro-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 346$ (MH^+)

Example 242

(5-Fluoro-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 5-Fluoro-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 389, 391$ (MH^+)

Example 243

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,8-dimethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,8-Dimethyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 342$ (MH^+)

Example 244

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,8-dimethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,8-Dimethyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 385, 387$ (MH^+)

Example 245

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,7-dimethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,7-Dimethyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 342$ (MH^+)

Example 246

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,7-dimethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,7-Dimethyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 385, 387$ (MH^+)

Example 247

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6-dimethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,6-Dimethyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 342$ (MH^+)

Example 248

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6-dimethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,6-Dimethyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 385, 387$ (MH^+)

Example 249

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,5-dimethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,5-Dimethyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 342$ (MH^+)

Example 250

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,5-dimethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1,5-Dimethyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 385, 387$ (MH^+)

Example 251

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methoxy-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-Methoxy-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 358$ (MH^+)

Example 252

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methoxy-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-Methoxy-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 401, 403$ (MH^+)

Example 253

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-methoxy-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 7-Methoxy-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 358$ (MH^+)

Example 254

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-methoxy-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 7-Methoxy-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 401, 403$ (MH^+)

Example 255

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-methoxy-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Methoxy-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 358$ (MH^+)

Example 256

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-methoxy-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Methoxy-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 401, 403$ (MH^+)

Example 257

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-methoxy-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 5-Methoxy-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 358$ (MH^+)

Example 258

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-methoxy-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 5-Methoxy-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 401, 403$ (MH^+)

Example 259

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-8-trifluoromethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-8-trifluoromethyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 342$ (MH^+)

Example 260

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-8-trifluoromethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-8-trifluoromethyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 385, 387$ (MH^+)

Example 261

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-trifluoromethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-7-trifluoromethyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 342$ (MH^+)

Example 262

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-trifluoromethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-7-trifluoromethyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 385, 387$ (MH^+)

Example 263

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-trifluoromethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-6-trifluoromethyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 342$ (MH^+)

Example 264

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-trifluoromethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-6-trifluoromethyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 385, 387$ (MH^+)

Example 265

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-5-trifluoromethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-5-trifluoromethyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 342$ (MH^+)

Example 266

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-5-trifluoromethyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-5-trifluoromethyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 385, 387$ (MH^+)

Example 267

N-[2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-cinnolin-8-yl]-acetamide

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with N-(1-Methyl-1,2,3,4-tetrahydro-cinnolin-8-yl)-acetamide to provide the title compound in good to moderate yield.

LC/MS: $m/z = 385$ (MH^+)

Example 268

N-[2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-cinnolin-8-yl]-acetamide

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with N-(1-Methyl-1,2,3,4-tetrahydro-cinnolin-8-yl)-acetamide to provide the title compound in good to moderate yield.

LC/MS: $m/z = 428, 430$ (MH^+)

Example 269

N-[2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-cinnolin-7-yl]-acetamide

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with N-(1-Methyl-1,2,3,4-tetrahydro-cinnolin-7-yl)-acetamide to provide the title compound in good to moderate yield.

LC/MS: $m/z = 385$ (MH^+)

Example 270

N-[2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-cinnolin-7-yl]-acetamide

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with N-(1-Methyl-1,2,3,4-tetrahydro-cinnolin-7-yl)-acetamide to provide the title compound in good to moderate yield.

LC/MS: $m/z = 428, 430$ (MH^+)

Example 271

N-[2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-cinnolin-6-yl]-acetamide

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with N-(1-Methyl-1,2,3,4-tetrahydro-cinnolin-6-yl)-acetamide to provide the title compound in good to moderate yield.

LC/MS: $m/z = 385$ (MH^+)

Example 272

N-[2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-cinnolin-6-yl]-acetamide

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with N-(1-Methyl-1,2,3,4-tetrahydro-cinnolin-6-yl)-acetamide to provide the title compound in good to moderate yield.

LC/MS: $m/z = 428, 430$ (MH^+)

Example 273

N-[2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-cinnolin-5-yl]-acetamide

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with N-(1-Methyl-1,2,3,4-tetrahydro-cinnolin-5-yl)-acetamide to provide the title compound in good to moderate yield.

LC/MS: $m/z = 385$ (MH^+)

Example 274

N-[2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-cinnolin-5-yl]-acetamide

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with N-(1-Methyl-1,2,3,4-tetrahydro-cinnolin-5-yl)-acetamide to provide the title compound in good to moderate yield.

LC/MS: $m/z = 428, 430$ (MH^+)

Example 275

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methanesulfonyl-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-Methanesulfonyl-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 407$ (MH^+)

Example 276

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methanesulfonyl-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-Methanesulfonyl-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 449, 451$ (MH^+)

Example 277

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-methanesulfonyl-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 7-Methanesulfonyl-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 407$ (MH^+)

Example 278

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-methanesulfonyl-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 7-Methanesulfonyl-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 449, 451$ (MH^+)

Example 279

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-methanesulfonyl-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Methanesulfonyl-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 407$ (MH^+)

Example 280

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-methanesulfonyl-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Methanesulfonyl-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 449, 451$ (MH^+)

Example 281

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-methanesulfonyl-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 5-Methanesulfonyl-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 407$ (MH^+)

Example 282

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-methanesulfonyl-1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 5-Methanesulfonyl-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 449, 451$ (MH^+)

Example 283

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-pyrido[2,3-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-1,2,3,4-tetrahydro-pyrido[2,3-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 330$ (MH^+)

Example 284

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-pyrido[2,3-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-1,2,3,4-tetrahydro-pyrido[2,3-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 372, 374$ (MH^+)

Example 285

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-pyrido[3,4-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-1,2,3,4-tetrahydro-pyrido[3,4-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 330$ (MH^+)

Example 286

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-pyrido[3,4-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-1,2,3,4-tetrahydro-pyrido[3,4-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 372, 374$ (MH^+)

Example 287

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-pyrido[4,3-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-1,2,3,4-tetrahydro-pyrido[4,3-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 330$ (MH^+)

Example 288

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-pyrido[4,3-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-1,2,3,4-tetrahydro-pyrido[4,3-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 372, 374$ (MH^+)

Example 289

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-pyrido[3,2-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-1,2,3,4-tetrahydro-pyrido[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 330$ (MH^+)

Example 290

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-pyrido[3,2-c]pyridazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-1,2,3,4-tetrahydro-pyrido[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 372, 374$ (MH^+)

Example 291

(7-Bromo-1-methyl-3,4-dihydro-1H-pyrido[3,2-c]pyridazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 7-Bromo-1-methyl-1,2,3,4-tetrahydro-pyrido[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 409$ (MH^+)

Example 292

(7-Bromo-1-methyl-3,4-dihydro-1H-pyrido[3,2-c]pyridazin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 7-Bromo-1-methyl-1,2,3,4-tetrahydro-pyrido[3,2-c]pyridazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 454$ (MH^+)

Example 293

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-8-pyridin-4-yl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-8-pyridin-4-yl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 406$ (MH^+)

Example 294

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-8-pyridin-4-yl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-8-pyridin-4-yl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 448, 450$ (MH^+)

Example 295

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-pyridin-4-yl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-7-pyridin-4-yl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 406$ (MH^+)

Example 296

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-pyridin-4-yl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-7-pyridin-4-yl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 448, 450$ (MH^+)

Example 297

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyridin-4-yl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-6-pyridin-4-yl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 406$ (MH^+)

Example 298

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyridin-4-yl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-6-pyridin-4-yl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 448, 450$ (MH^+)

Example 299

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-5-pyridin-4-yl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-5-pyridin-4-yl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 406$ (MH^+)

Example 300

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-5-pyridin-4-yl-3,4-dihydro-1H-cinnolin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-5-pyridin-4-yl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 448, 450$ (MH^+)

Example 301

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[8-(2-fluoro-pyridin-4-yl)-1-methyl-3,4-dihydro-1H-cinnolin-2-yl]-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-(2-Fluoro-pyridin-4-yl)-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 424$ (MH^+)

Example 302

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[8-(2-fluoro-pyridin-4-yl)-1-methyl-3,4-dihydro-1H-cinnolin-2-yl]-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 8-(2-Fluoro-pyridin-4-yl)-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 466, 468$ (MH^+)

Example 303

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[7-(2-fluoro-pyridin-4-yl)-1-methyl-3,4-dihydro-1H-cinnolin-2-yl]-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 7-(2-Fluoro-pyridin-4-yl)-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 424$ (MH^+)

Example 304

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[7-(2-fluoro-pyridin-4-yl)-1-methyl-3,4-dihydro-1H-cinnolin-2-yl]-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 7-(2-Fluoro-pyridin-4-yl)-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 466, 468$ (MH^+)

Example 305

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[6-(2-fluoro-pyridin-4-yl)-1-methyl-3,4-dihydro-1H-cinnolin-2-yl]-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-(2-Fluoro-pyridin-4-yl)-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 424$ (MH^+)

Example 306

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[6-(2-fluoro-pyridin-4-yl)-1-methyl-3,4-dihydro-1H-cinnolin-2-yl]-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-(2-Fluoro-pyridin-4-yl)-1-methyl-

1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 466, 468$ (MH^+)

Example 307

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[5-(2-fluoro-pyridin-4-yl)-1-methyl-3,4-dihydro-1H-cinnolin-2-yl]-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 5-(2-Fluoro-pyridin-4-yl)-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 424$ (MH^+)

Example 308

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[5-(2-fluoro-pyridin-4-yl)-1-methyl-3,4-dihydro-1H-cinnolin-2-yl]-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 5-(2-Fluoro-pyridin-4-yl)-1-methyl-1,2,3,4-tetrahydro-cinnoline to provide the title compound in good to moderate yield.

LC/MS: $m/z = 466, 468$ (MH^+)

Example 309

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-imidazo[2,1-c][1,2,4]triazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-1,2,3,4-tetrahydro-imidazo[2,1-c][1,2,4]triazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 319$ (MH^+)

Example 310

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-imidazo[2,1-c][1,2,4]triazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-Methyl-1,2,3,4-tetrahydro-imidazo[2,1-c][1,2,4]triazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 361, 363$ (MH^+)

Example 311

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dibromo-1-methyl-3,4-dihydro-1H-imidazo[2,1-c][1,2,4]triazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6,7-Dibromo-1-methyl-1,2,3,4-tetrahydro-imidazo[2,1-c][1,2,4]triazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 477$ (MH^+)

Example 312

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dibromo-1-methyl-3,4-dihydro-1H-imidazo[2,1-c][1,2,4]triazin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6,7-Dibromo-1-methyl-1,2,3,4-tetrahydro-imidazo[2,1-c][1,2,4]triazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 522$ (MH^+)

Example 313

(6-Bromo-1-methyl-3,4-dihydro-1H-imidazo[2,1-c][1,2,4]triazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Bromo-1-methyl-1,2,3,4-tetrahydro-imidazo[2,1-c][1,2,4]triazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 399$ (MH^+)

Example 314

(6-Bromo-1-methyl-3,4-dihydro-1H-imidazo[2,1-c][1,2,4]triazin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 6-Bromo-1-methyl-1,2,3,4-tetrahydro-imidazo[2,1-c][1,2,4]triazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 443$ (MH^+)

Example 315

(7-Bromo-1-methyl-3,4-dihydro-1H-imidazo[2,1-c][1,2,4]triazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 7-Bromo-1-methyl-1,2,3,4-tetrahydro-imidazo[2,1-c][1,2,4]triazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 399$ (MH^+)

Example 316

(7-Bromo-1-methyl-3,4-dihydro-1H-imidazo[2,1-c][1,2,4]triazin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

In close analogy to the procedure described in Example 181, 6-bromo-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 7-Bromo-1-methyl-1,2,3,4-tetrahydro-imidazo[2,1-c][1,2,4]triazine to provide the title compound in good to moderate yield.

LC/MS: $m/z = 443$ (MH^+)

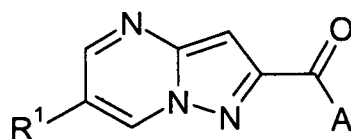
Example 317

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-7-(2H-tetrazol-5-yl)-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-methanone

In close analogy to the procedure described in Example 181, 6-chloro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid is reacted with 1-methyl-7-(2H-tetrazol-5-yl)-1,2,3,4-tetrahydro-pyrrolo[1,2-a]pyrazine to provide the title compound in good to moderate yield.

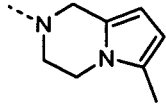
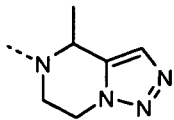
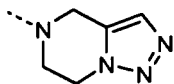
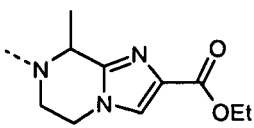
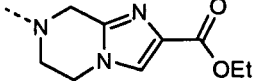
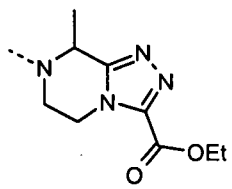
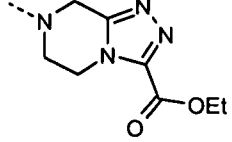
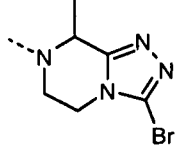
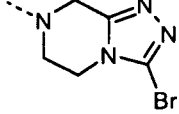
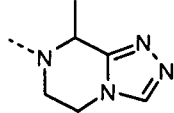
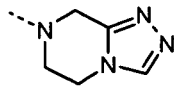
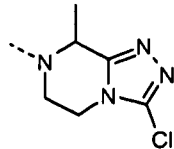
LC/MS: $m/z = 384$ (MH^+)

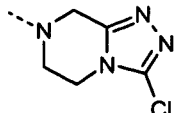
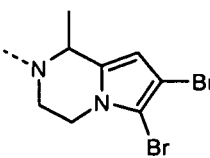
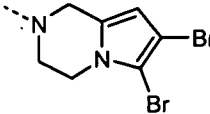
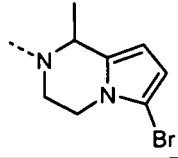
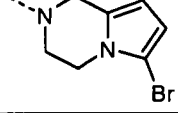
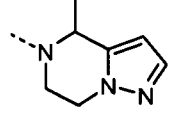
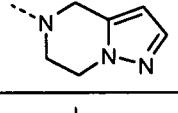
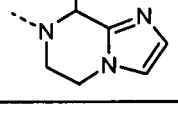
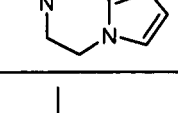
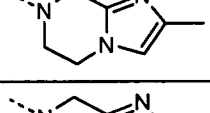
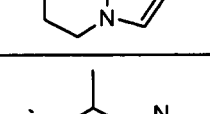
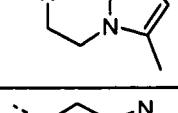
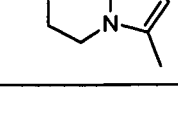
Table 1

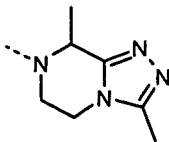
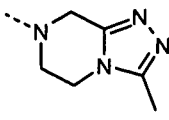
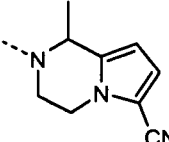
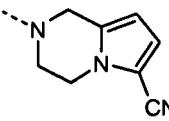
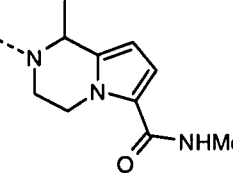
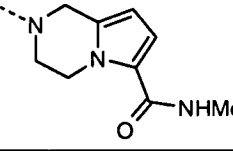
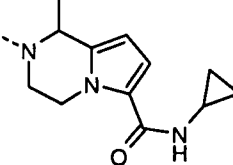
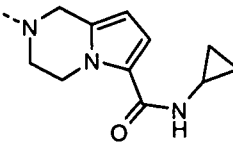
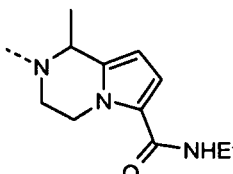
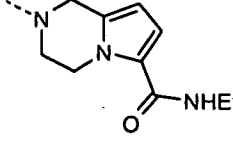


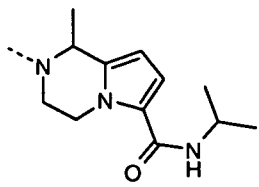
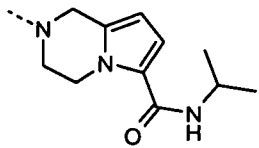
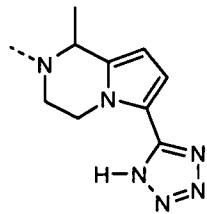
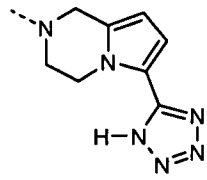
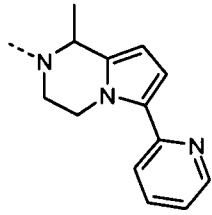
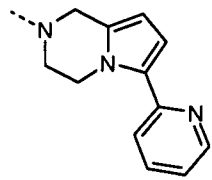
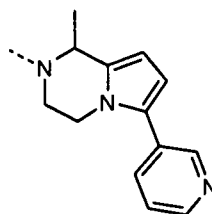
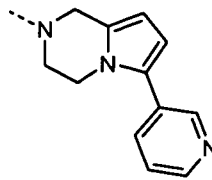
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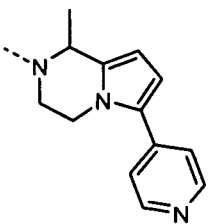
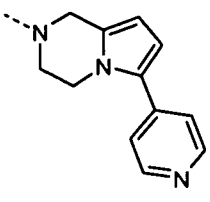
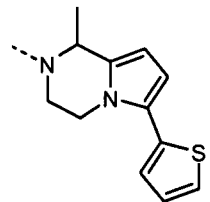
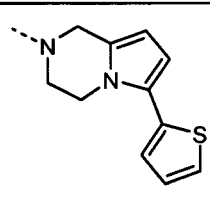
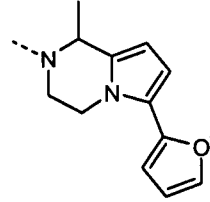
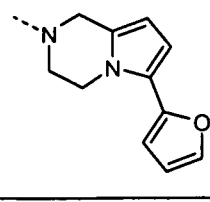
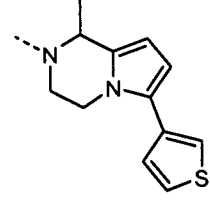
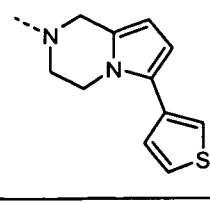
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2	Cl	
4	Br	
5	Cl	
7	Br	

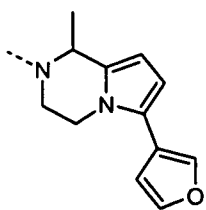
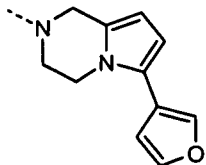
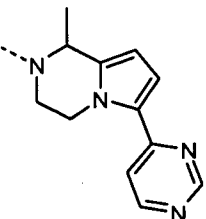
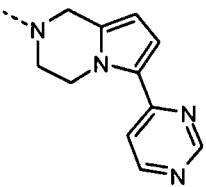
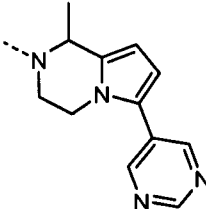
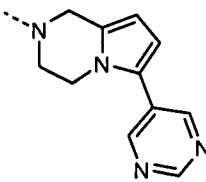
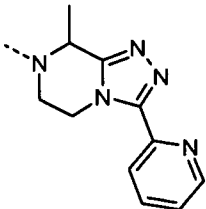
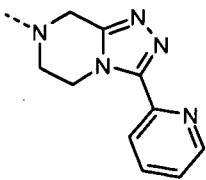
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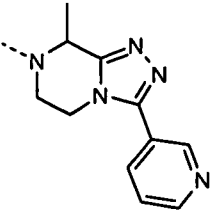
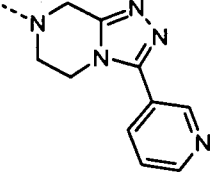
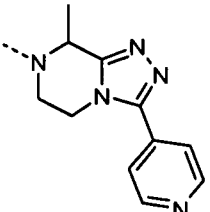
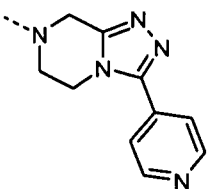
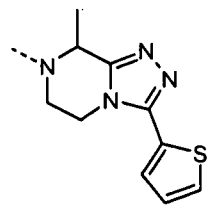
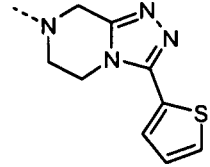
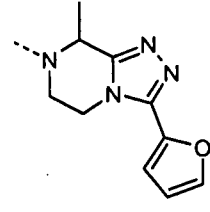
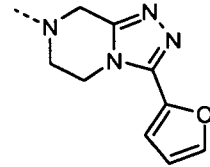
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56	Br	

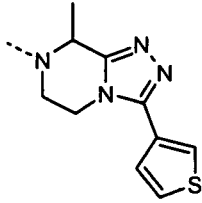
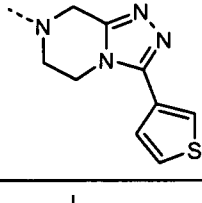
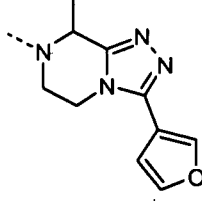
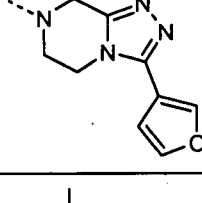
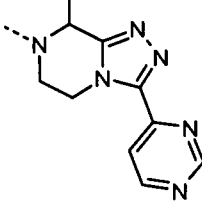
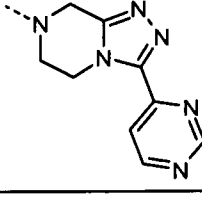
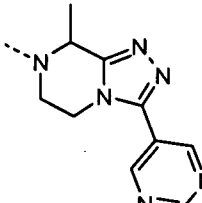
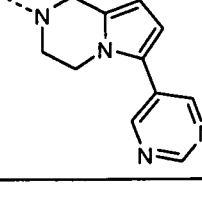
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76	Br	

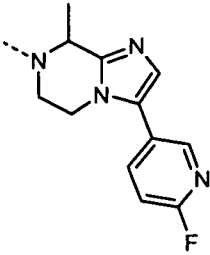
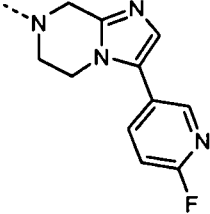
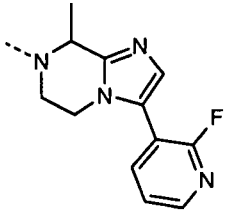
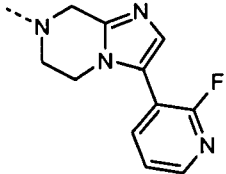
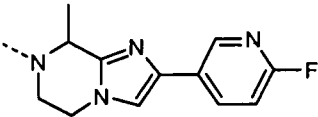
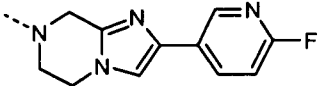
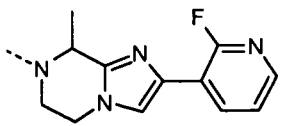
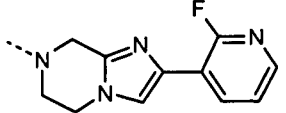
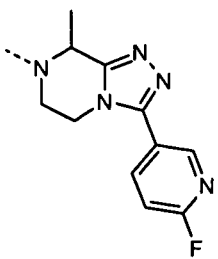
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92	Br	

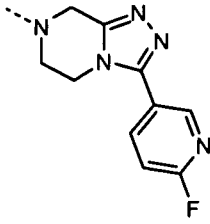
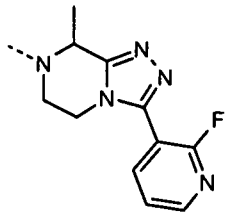
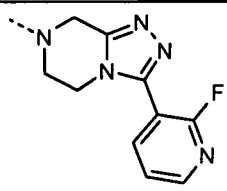
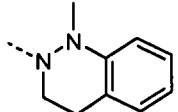
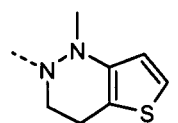
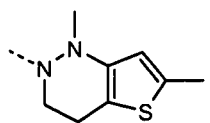
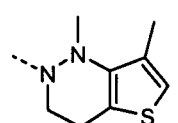
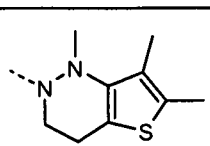
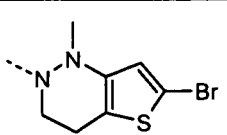
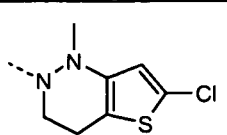
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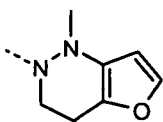
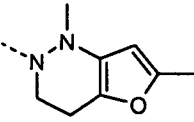
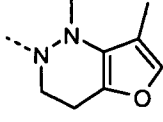
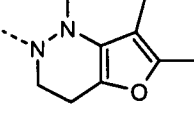
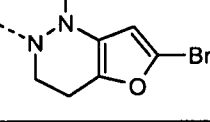
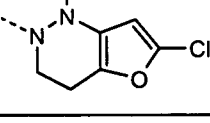
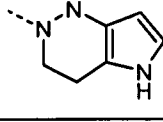
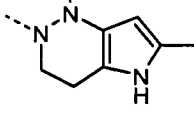
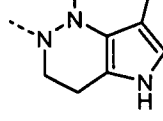
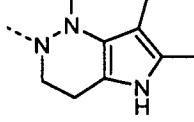
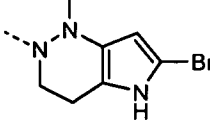
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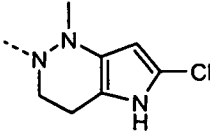
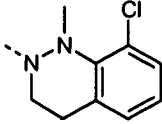
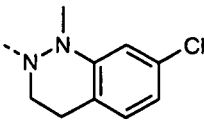
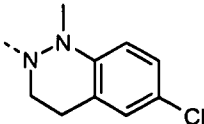
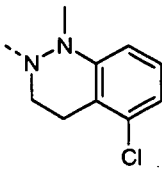
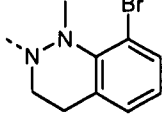
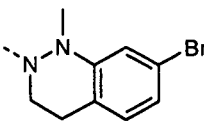
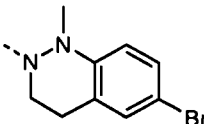
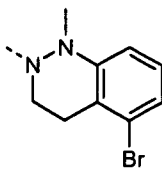
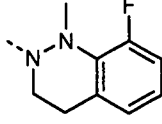
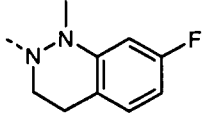
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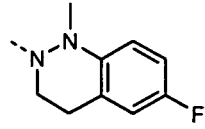
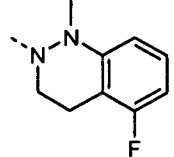
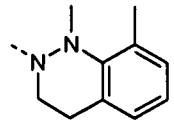
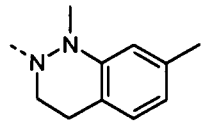
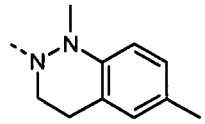
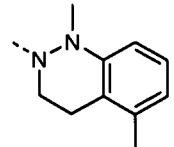
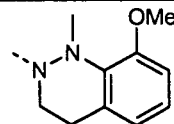
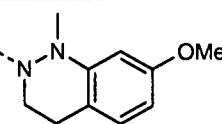
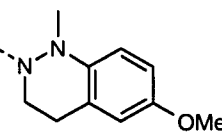
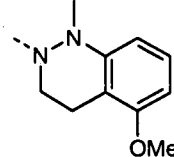
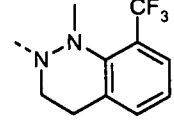
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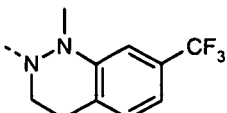
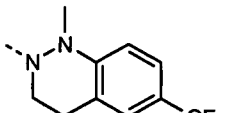
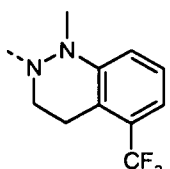
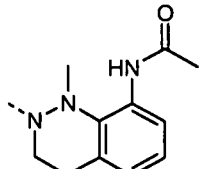
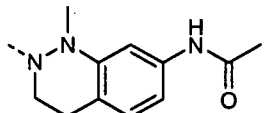
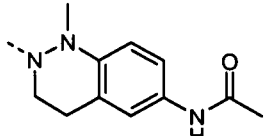
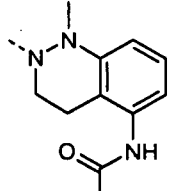
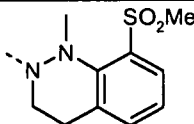
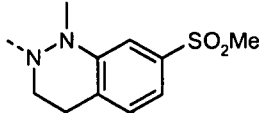
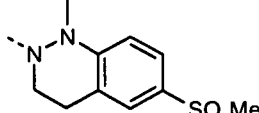
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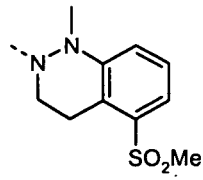
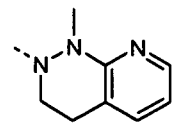
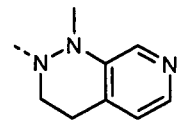
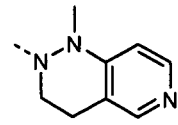
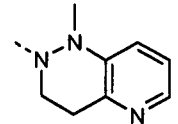
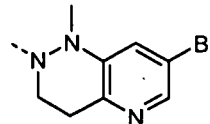
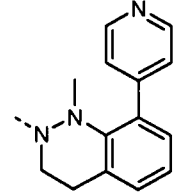
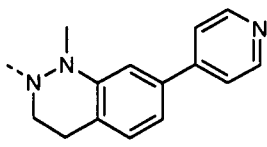
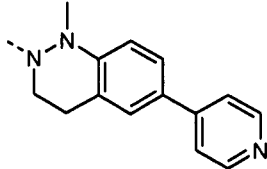
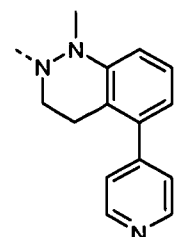
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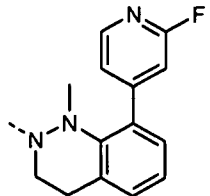
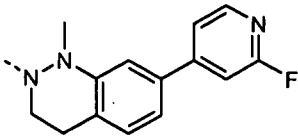
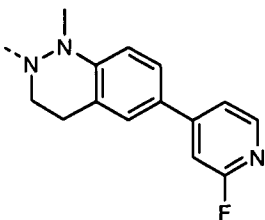
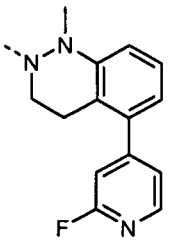
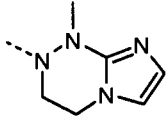
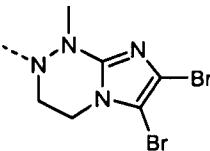
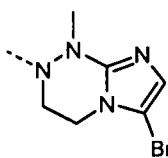
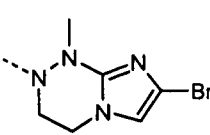
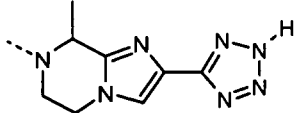
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317	Cl	

Examples of Representative Pharmaceutical Compositions

With the aid of commonly used solvents, auxiliary agents and carriers, the reaction products can be processed into tablets, coated tablets, capsules, drip solutions, suppositories, injection and infusion preparations, and the like and can be therapeutically applied by the oral, rectal, parenteral, and additional routes. Representative pharmaceutical compositions according to the present invention follow:

- (a) Tablets suitable for oral administration which contain the active ingredient, may be prepared by conventional tableting techniques.
- (b) For suppositories, any usual suppository base may be employed for incorporation therein by usual procedure of the active ingredient, such as a polyethyleneglycol which is a solid at normal room temperature but which melts at or about body temperature.
- (c) For parental (including intravenous and subcutaneous) sterile solutions, the active ingredient together with conventional ingredients in usual amounts are employed, such as for example sodium chloride and double-distilled water q.s., according to conventional procedure, such as filtration, aseptic filling into ampoules or IV-drip bottles, and autoclaving for sterility.

Other suitable pharmaceutical compositions will be immediately apparent to one skilled in the art.

Formulation Examples for the compounds of Formula I:

The following examples are given by way of illustration. As active ingredient, the compound according to example 76 can be used.

Example 1 Tablet Formulation

A suitable formulation for a tablet containing 10 milligrams of active ingredient is as follows:

	mg
Active Ingredient	10
Lactose	61
Microcrystalline Cellulose	25
Talcum	2
Magnesium stearate	1
Colloidal silicon dioxide	1

Example 2 Coated Tablet Formulation

Another suitable formulation for a tablet containing 100 mg is as follows:

	mg
Active Ingredient	100
Polyvinylpyrrolidone, crosslinked	10
Potato starch	20
Polyvinylpyrrolidone	19
Magnesium stearate	1
Microcrystalline Cellulose	50
Film coated and colored.	
The film coating material consists of:	
Hypromellose	10
Microcryst. Cellulose	5
Talcum	5
Polyethylene glycol	2
Color pigments	5

Example 3 Capsule Formulation

A suitable formulation for a capsule containing 50 milligrams of active ingredient is as follows:

	mg
Active Ingredient	50
Corn starch	26
Dibasic calcium phosphate	50
Talcum	2
Colloidal silicon dioxide	2

This formulation is filled in a gelatin capsule.

Example 4 Solution for injection

A suitable formulation for an injectable solution is as follows:

Active Ingredient	mg	10
Sodium chloride	mg	q.s.
Water for Injection	ml	add 1.0

Example 5 Liquid oral formulation

A suitable formulation for 1 liter of an oral solution containing 2 milligrams of active ingredient in one milliliter of the mixture is as follows:

	mg
Active Ingredient	2
Saccharose	250
Glucose	300
Sorbitol	150
Orange flavor	10
Colorant	q.s.
Purified water	add 1000 ml

Example 6 Liquid oral formulation

Another suitable formulation for 1 liter of a liquid mixture containing 20 milligrams of active ingredient in one milliliter of the mixture is as follows:

	g
Active Ingredient	20.00
Tragacanth	7.00
Glycerol	50.00
Saccharose	400.00
Methylparaben	0.50
Propylparaben	0.05
Black currant-flavor	10.00
Soluble Red color	0.02
Purified water	add 1000 ml

Example 7 Liquid oral formulation

Another suitable formulation for 1 liter of a liquid mixture containing 2 milligrams of active ingredient in one milliliter of the mixture is as follows:

	g
Active Ingredient	2
Saccharose	400
Bitter orange peel tincture	20
Sweet orange peel tincture	15
Purified water	add 1000 ml

Example 8 Aerosol formulation

180 g of the aerosol solution contain:

	g
Active Ingredient	10
Oleic acid	5
Ethanol	81
Purified Water	9

Tetrafluoroethane

75

15 ml of the solution are filled into aluminum aerosol cans, capped with a dosing valve, purged with 3.0 bar.

Example 9 Trans-Dermal-System formulation

100 g of the solution contain:

	g
Active Ingredient	10.0
Ethanol	57.5
Propyleneglycol	7.5
Dimethylsulfoxide	5.0
Hydroxyethylcellulose	0.4
Purified water	19.6

1.8 ml of the solution is placed on a fleece covered by an adhesive backing foil. The system is closed by a protective liner which will be removed before use.

Example 10 Nanoparticle formulation

10 g of polybutylcyanoacrylate nanoparticles contain:

	g
Active Ingredient	1.00
Poloxamer	0.10
Butylcyanoacrylate	8.75
Mannitol	0.10
Sodium chloride	0.05

Polybutylcyanoacrylate nanoparticles are prepared by emulsion polymerization in a water/0.1 N HCl/ethanol mixture as polymerization medium. The nanoparticles in the suspension are finally lyophilized under vacuum.

Example 11 Suspension formulation

1.0 g of the suspension contains the following:

	g
Active Ingredient	0.10
Hypromellose	0.01
Purified water	Ad 1.0 g

Hypromellose is dispersed in water homogeneously with a high speed mixer/blender. After about one hour of hydration time of the hypromellose, the active ingredient is blended homogeneously into the hypromellose solution. The viscosity of the suspension can be adjusted by the amount of hypromellose, resulting in a very stable suspension with a very slow tendency of particle sedimentation and particle agglomeration.

Example 12 Solution for Injection

1.0 ml of solution contain:

	g
Active Ingredient	0.05
Mannitol	q.s.
DMSO	0.10
Water for injection	Ad 1.0 ml

The active ingredient is dissolved in DMSO by stirring and heating (solution 1). The mannitol is dissolved in WFI (solution 2). After cooling down to room temperature solution 1 is mixed with solution 2 by continuous stirring. The solution is sterilized by filtration of by autoclaving.

Pharmacology

The active principles of the present invention, and pharmaceutical compositions containing them and method of treating therewith, are characterized by unique and advantageous properties. The compounds and pharmaceutical compositions thereof exhibit, in standard accepted reliable test procedures, the following valuable properties and characteristics

METHODS

Binding Assays for the Characterization of mGluR5 Antagonists

[³H]-MPEP (2-methyl-6-(phenylethynyl)pyridine) binding to transmembrane allosteric modulatory sites of mGluR5 receptors in cortical membranes.

Preparation of rat cortical membranes:

Male Sprague-Dawley rats (200-250 g) are decapitated and their brains are removed rapidly. The cortex is dissected and homogenized in 20 volumes of ice-cold 0.32 M sucrose using a glass-Teflon homogenizer. The homogenate is centrifuged at 1000 x g for 10 minutes. The pellet is discarded and the supernatant centrifuged at 20,000 x g for 20 minutes. The resulting pellet is re-suspended in 20 volumes of distilled water and centrifuged for 20 minutes at 8000 x g. Then the supernatant and the buffy coat are centrifuged at 48,000 x g for 20 minutes in the presence of 50 mM Tris-HCl, pH 8.0. The pellet is then re-suspended and centrifuged two to three more times at 48,000 x g for 20 minutes in the presence of 50 mM Tris-HCl, pH 8.0. All centrifugation steps are carried out at 4°C. After resuspension in 5 volumes of 50 mM Tris-HCl, pH 8.0 the membrane suspension is frozen rapidly at -80°C.

On the day of assay the membranes are thawed and washed four times by resuspension in 50 mM Tris-HCl, pH 8.0 and centrifugation at 48,000 x g for 20 minutes and finally re-suspended in 50 mM Tris-HCl, pH 7.4. The amount of protein in the final membrane preparation (500-700 µg/ml) is determined according to the method of Lowry (Lowry O. H. et al. 1951. J. Biol. Chem. 193, 256-275).

[³H]-MPEP Assay

Incubations are started by adding [³H]-MPEP (50.2 Ci/mmol, 5 nM, Tocris, GB) to vials with 125-250 µg protein (total volume 0.25 ml) and various concentrations of the agents.

Alternatively, assays are performed with [³H]-MMPEP (2-(3-methoxyphenylethynyl)-6-methylpyridine hydrochloride) as radioligand. The incubations are continued at room temperature for 60 minutes (equilibrium is achieved under the conditions used). Non-specific binding is defined by the addition of unlabeled MPEP (10 µM). Incubations are terminated using a Millipore filter system. The samples are rinsed twice with 4 ml of ice-cold assay buffer over glass fibre filters (Schleicher & Schuell, Germany) under a constant vacuum. Following separation and rinse, the filters are placed into scintillation liquid (5 ml Ultima Gold, Perkin Elmer, Germany) and radioactivity retained on the filters is determined with a conventional liquid scintillation counter (Canberra Packard, Germany).

Characterization:

Specific binding is extremely high i.e. normally > 85% and essentially independent of buffer (Tris or HEPES both 50 mM) and pH (6.8-8.9). There is a clear saturable protein dependence and the chosen protein concentration used for subsequent assays (500-700 µg/ml) is within the linear portion of this dependence. Cold MPEP displaces hot ligand with an IC₅₀ of 11.2 ± 0.64 nM. The K_d of [³H]-MPEP of 13.6 nM is determined by Scatchard analysis and used according to the Cheng Prusoff relationship to calculate the affinity of displacers as K_d values (IC₅₀ of cold MPEP equates to a K_i of 8.2 nM). B_{max} is 0.56 pm / mg protein.

Functional Assays of mGluR5 Receptors

Cytosolic Calcium studies with stably transfected cells:

Chinese hamster ovary cells (CHO-K1 cells), stably transfected for inducible expression of a human metabotropic glutamate receptor mGluR5, are seeded into black clear bottom 96 well plates at a density of 35.000 cells per well. The standard growth medium used (Dulbecco's modified Eagle Medium, DMEM plus L-proline)

contains the appropriate inducer isopropyl- β -D-thiogalactopyranosid (IPTG) to achieve optimal receptor expression. One day after seeding the growth medium is exchanged for reconstituted Ca-Kit (Molecular Devices, USA) and incubated for one hour. Ca-Kit is reconstituted in an assay buffer containing 20 mM HEPES pH 7.4, glutamic-pyruvate transaminase, pyridoxal phosphate and sodium pyruvate in Hank's balanced salt solution (HBBS). Agonistic compounds to the receptor elicit increases in cytosolic calcium which can be measured as increases in fluorescence signals by use of a fluorescence imaging plate reader (Molecular Devices). To analyze their potency to modulate the Ca-response test compounds, dissolved in a final DMSO concentration of 0.5%, are added on-line 5 minutes before the agonist to the receptor (L-quisqualic acid at a concentration giving ~80% of the maximal signal).

Astrocyte culture:

Primary astrocyte cultures are prepared from cortices of newborn rats as described by Booher and Sensenbrenner (1972, *Neurobiology* 2(3):97-105). Briefly, Sprague-Dawley rat pups (2 - 4 d old) are decapitated and neocortices are dissected, disintegrated with a nylon filter (pore size 80 μ m) and carefully triturated. The cell suspension is plated on poly-D-lysine pre-coated flasks (Costar, Netherlands) and cultivated in Dulbecco's Modified Eagle's Medium (DMEM, Invitrogen, Germany) supplemented with 10% foetal calf serum (FCS, Sigma, Germany), 4 mM glutamine and 50 μ g/ml gentamycin (both Biochrom, Germany) at 37°C in a humidified atmosphere of 5% CO₂ / 95% air for 7 d with exchanging the medium at day 2 and 6.

After 7 days in vitro (DIV), cells are shaken overnight at 250 rpm to remove oligodendrocytes and microglia. The next day, astrocytes are rinsed twice with CMF-PBS (calcium- and magnesium-free phosphate buffered saline, Biochrom, Germany), trypsinized and subplated on poly-D-lysine pre-coated 96-well plates (Greiner, Germany) at a density of 40,000 cells/well. 24 h after establishing the secondary culture the astrocytes are rinsed with PBS⁺⁺ (phosphate buffered saline, Biochrom, Germany) and fed with astrocyte-defined medium (ADM) consisting of DMEM containing 1x G5-supplement (Invitrogen, Germany), 0.5 μ g/ml heparan sulfate, and 1.5 μ g/ml fibronectin (both Sigma, Germany) (Miller et al., (1993)

Brain Res. 618(1):175-8). 3 d later the medium is exchanged and the cells incubated for another 2-3 d, so that at the time of experiments astrocytes are 14-15 DIV.

Immunocytochemistry

Immunostaining is performed to confirm the presence of astrocytic markers such as the glial fibrillary acidic protein (GFAP) as well as to monitor the expression of mGluR5 receptors.

Cytosolic Calcium studies with astrocytes:

The increase of cytosolic calcium after stimulation with the mGluR5 agonist L-quisqualate is measured using a fluorometric imaging plate reader (FLIPR) and the Ca-Kit (both Molecular Devices). Prior to addition of agonist or antagonist the medium is aspirated and cells are loaded for 2 h at RT with 150 μ l of loading buffer consisting of Ca-sensitive dye reconstituted in sodium chloride (123 mM), potassium chloride (5.4 mM), magnesium chloride (0.8 mM), calcium chloride (1.8 mM), D-glucose (15 mM), and HEPES (20 mM), pH 7.3. Subsequently, plates are transferred to FLIPR to detect calcium increase with the addition of L-quisqualate (100 nM) measured as relative fluorescence units (RFU). If antagonists are tested, these compounds are pre-incubated for 10 minutes at RT before addition of the respective agonist.

For positive modulators, concentration-response curves for quisqualate are performed in the presence and absence of 10 μ M modulator to determine the extent of potentiation / agonist potency increase. Thereafter, concentration-response curves for the positive modulator are performed in the presence of a fixed concentration of quisqualate showing the biggest window for potentiation (normally 10-30 nM).

Data analysis

The fluorescence signal increase after addition of agonist reflects the increase of cytosolic calcium. Inconsistencies in the amount of cells per well are normalised by using the spatial uniformity correction of the FLIPR software. The mean of

replicated temporal data (n=3-5) is calculated and used for graphical representation. For the evaluation of the pharmacology, the calcium changes in response to different concentrations of agonist or antagonist are determined using a maximum minus minimum (MaxMin) calculation.

All responses (RFU-values) are determined as percentage of control (= maximum response). EC₅₀ and IC₅₀ are calculated according the logistic equation using GraFit 5.0 (Erithacus Software, GB) or Prism 4.0 (GraphPad Software, USA). The compounds of the present invention have a potency (IC₅₀) within a range of about 0.5 nM to about 100 μ M.

Results for representative compounds of the invention are shown in Tables A1-A3.

In conclusion, from the foregoing, it is apparent that the present invention provides novel and valuable applications and uses of the compounds of the present invention, which compounds comprise the active principle according to the present invention, as well as novel pharmaceutical compositions thereof and methods of preparation thereof and of treating therewith.

The high order of activity of the active agent of the present invention and compositions thereof, as evidenced by the tests reported, is indicative of utility based on its valuable activity in human beings as well as in lower animals. Clinical evaluation in human beings has not been completed. It will be clearly understood that the distribution and marketing of any compound or composition falling within the scope of the present invention for use in human beings will of course have to be predicated upon prior approval by governmental agencies which are responsible for and authorized to pass judgment on such questions.

The instant compounds of Formula I represent a novel class of mGluR5 modulators. In view of their potency, they will be useful therapeutics in a wide range of disorders, in particular CNS disorders, which involve excessive glutamate induced excitation.

These compounds accordingly find application in the treatment of the disorders of a living animal body, especially a human, as listed earlier in the description.

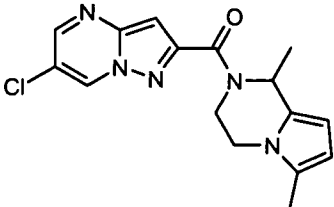
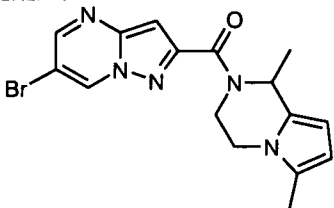
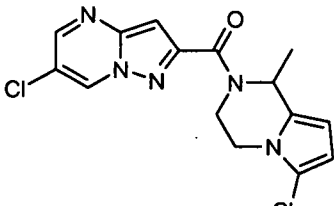
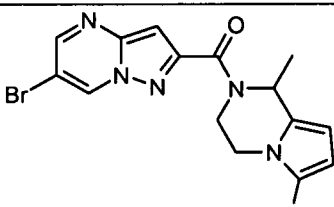
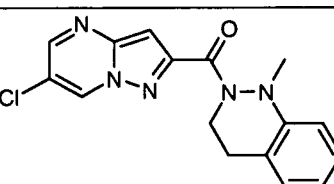
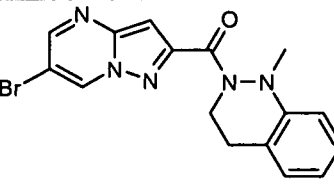
These compounds also find application in the treatment of indications in a living animal body, especially a human, wherein a particular condition does not necessarily exist but wherein a particular physiological parameter may be improved through administration of the instant compounds, including cognitive enhancement.

Neuroprotection as well as cognitive enhancement can also be achieved by combining application of these compounds with NMDA receptor antagonists like Memantine and Neramexane.

The method-of-treating a living animal body with a compound of the invention, for the inhibition of progression or alleviation of the selected ailment therein, is as previously stated by any normally-accepted pharmaceutical route, employing the selected dosage which is effective in the alleviation of the particular ailment desired to be alleviated. Use of the compounds of the present invention in the manufacture of a medicament for the treatment of a living animal for inhibition of progression or alleviation of selected ailments or conditions, particularly ailments or conditions susceptible to treatment with a Group I mGluR modulator is carried out in the usual manner comprising the step of admixing an effective amount of a compound of the invention with a pharmaceutically-acceptable diluent, excipient, or carrier, and the method-of-treating, pharmaceutical compositions, and use of a compound of the present invention in the manufacture of a medicament.

Representative pharmaceutical compositions prepared by admixing the active ingredient with a suitable pharmaceutically-acceptable excipient, diluent, or carrier, include tablets, capsules, solutions for injection, liquid oral formulations, aerosol formulations, TDS formulations, and nanoparticle formulations, thus to produce medicaments for oral, injectable, or dermal use, also in accord with the foregoing.

Table A1 (Cytosolic Calcium studies with stably transfected cells)

Compound	Chemical name	mGluR5_FLIPR _h_CHO_NAM IC50 [μ M]
	(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6-dimethyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone	0.3273
	(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6-dimethyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone	0.2225
	(6-Chloro-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone	0.091
	(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-chloro-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone	0.0844
	(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone	0.1657
	(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone	0.1893

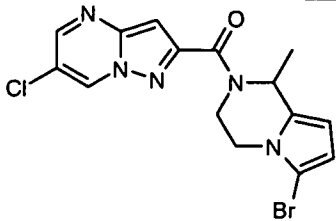
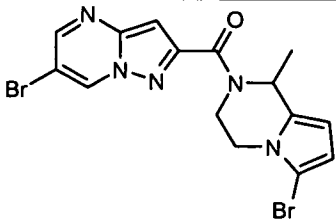
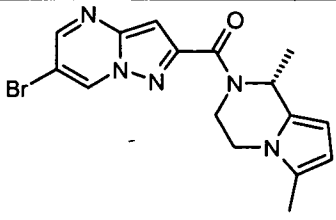
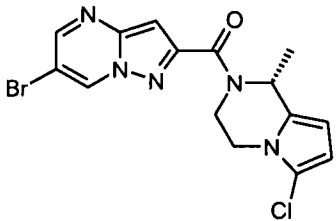
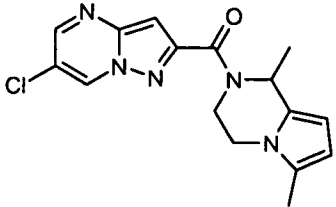
	(6-Bromo-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone	0.0342
	(6-Bromo-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone	0.0745
	(R)-(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6-dimethyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone	0.1183
	(R)-(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-chloro-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone	0.0245

Table A2 (Astrocyte culture test)

Compound	Chemical name	mGluR5_FLIP Rr_rpA IC50 [μM]
	(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6-dimethyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone	0.0873

	(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6-dimethyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone	0.0500
	(6-Chloro-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone	0.0219
	(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-chloro-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone	0.0225
	(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone	0.0823
	(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone	0.0637
	(6-Bromo-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone	0.0170
	(6-Bromo-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone	0.0150

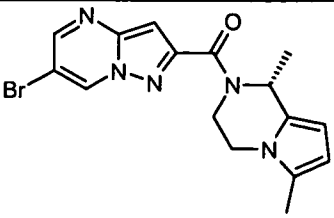
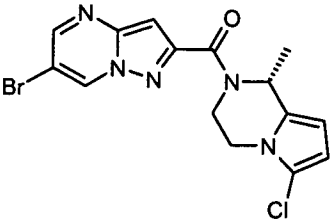
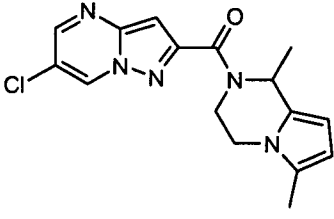
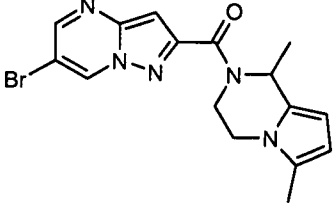
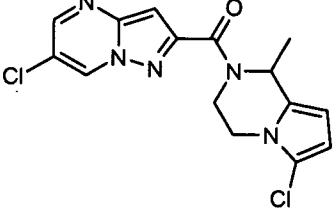
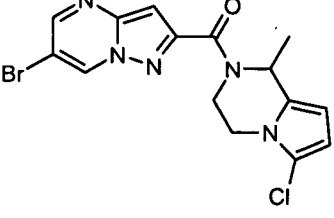
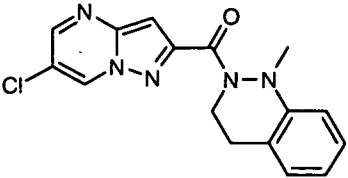
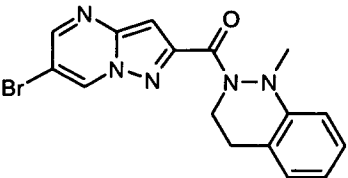
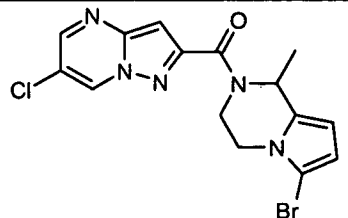
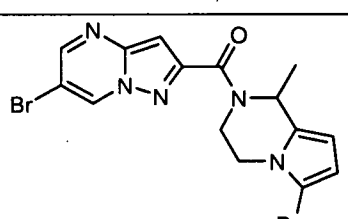
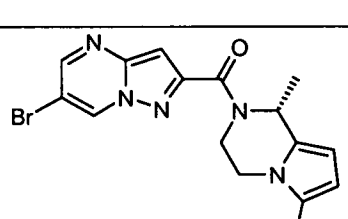
	(R)-(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6-dimethyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone	0.0343
	(R)-(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-chloro-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone	0.0078

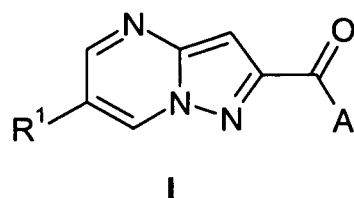
Table A3 (Results from ³H-MMPEP-Assay)

Compound	Chemical name	mGluR5_M-MPEP_r_CTX-IC50 [μM]
	(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6-dimethyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone	0.2745
	(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6-dimethyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone	0.2190
	(6-Chloro-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone	0.0420
	(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-chloro-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone	0.0445

	(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone	0.2470
	(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-cinnolin-2-yl)-methanone	0.2810
	(6-Bromo-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone	0.0730
	(6-Bromo-1-methyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone	0.0549
	(R)-(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,6-dimethyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazin-2-yl)-methanone	0.074

CLAIMS

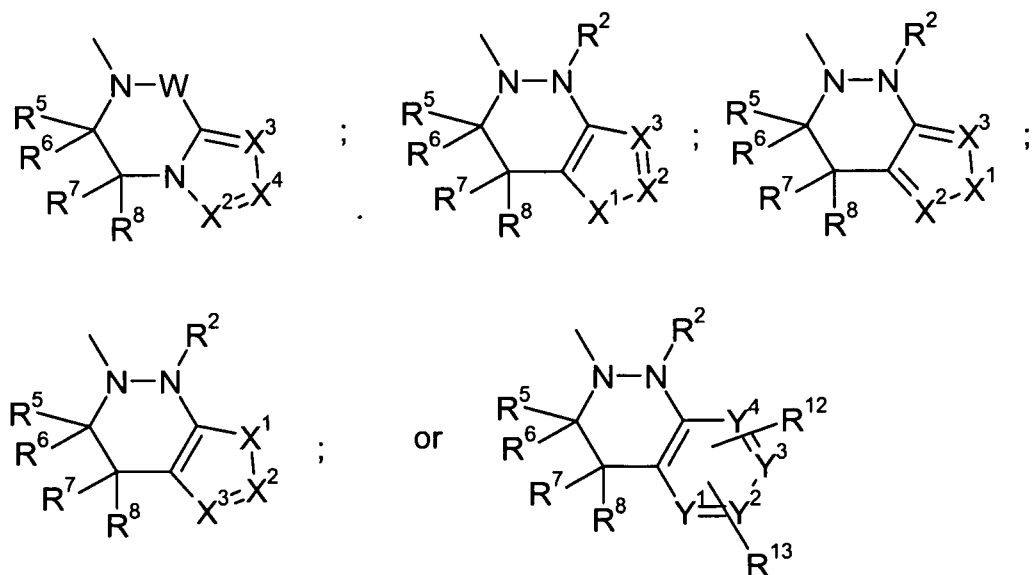
1. A compound selected from those of Formula I



wherein

R¹ represents chloro or bromo;

A represents



wherein

W represents NR² or CR³R⁴

R² represents hydrogen, C₁₋₆alkyl, trifluoromethyl or cycloC₃₋₁₂alkyl;

R³, R⁴, R⁵, R⁶, which may be the same or different, each independently represent hydrogen, C₁₋₆alkyl, cycloC₃₋₁₂alkyl, or trifluoromethyl;

R^7 , and R^8 , which may be the same or different, each independently represent hydrogen, C_{1-6} alkyl, cyclo C_{3-12} alkyl, amino, hydroxy, halogen, or trifluoromethyl;

X^1 represents CR^9R^{10} , NR^{11} , S, or O; and X^2 , X^3 , and X^4 , which may be the same or different each independently represent CR^9 or N, wherein

R^9 and R^{10} , which may be the same or different, each independently represent hydrogen, halogen, amino, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, aryl, C_{1-6} alkyl, cyclo C_{3-12} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, cyclo C_{3-12} alkyloxy, C_{2-6} alkenyloxy, C_{2-6} alkynyloxy, heteroaryl, heterocyclyl, aryloxy, heteroaryloxy, heterocyclyloxy, C_{1-6} alkylamino, di- C_{1-6} alkylamino, cyclo C_{3-12} alkylamino, di-cyclo C_{3-12} alkylamino, N- C_{1-6} alkyl-N-cyclo C_{3-12} alkylamino, C_{2-6} alkenylamino, C_{2-6} alkynylamino, di- C_{2-6} alkenylamino, di- C_{2-6} alkynylamino, N- C_{1-6} alkyl-N- C_{2-6} alkenylamino, N- C_{1-6} alkyl-N- C_{2-6} alkynylamino, N- C_{2-6} alkenyl-N-cyclo C_{3-12} alkylamino, N- C_{2-6} alkynyl-N-cyclo C_{3-12} alkylamino, N- C_{2-6} alkenyl-N- C_{2-6} alkynylamino, arylamino, diarylamino, aryl- C_{1-6} alkylamino, aryl- C_{2-6} alkenylamino, aryl- C_{2-6} alkynylamino, N-aryl-N-cyclo C_{3-12} alkylamino, heteroarylamino, diheteroarylamino, heteroaryl- C_{1-6} alkylamino, heteroaryl- C_{2-6} alkenylamino, heteroaryl- C_{2-6} alkynylamino, N-heteroaryl-N-cyclo C_{3-12} alkylamino, N-heteroaryl-N-arylamino, heterocyclylamino, diheterocyclylamino, heterocyclyl- C_{1-6} alkylamino, heterocyclyl- C_{2-6} alkenylamino, heterocyclyl- C_{2-6} alkynylamino, N-heterocyclyl-N-cyclo C_{3-12} alkylamino, N-heterocyclyl-N-arylamino, N-heterocyclyl-N-heteroarylamino, acyl, acyloxy, acylamino, C_{1-6} alkoxycarbonyl, cyclo C_{3-12} alkoxycarbonyl, C_{2-6} alkenyloxycarbonyl, C_{2-6} alkynyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, heterocyclyloxycarbonyl, aminocarbonyl, C_{1-6} alkylaminocarbonyl, di- C_{1-6} alkylaminocarbonyl, cyclo C_{3-12} alkylaminocarbonyl, di-cyclo C_{3-12} alkylaminocarbonyl, N- C_{1-6} alkyl-N-cyclo C_{3-12}

₁₂alkylaminocarbonyl, C₂₋₆alkenylaminocarbonyl, C₂₋₆alkynylaminocarbonyl, di-C₂₋₆alkenylaminocarbonyl, di-C₂₋₆alkynylaminocarbonyl, N-C₁₋₆alkyl-N-C₂₋₆alkenylaminocarbonyl, N-C₁₋₆alkyl-N-C₂₋₆alkynylaminocarbonyl, N-C₂₋₆alkenyl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-C₂₋₆alkynyl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-C₂₋₆alkenyl-N-C₂₋₆alkynylaminocarbonyl, arylaminocarbonyl, diarylaminocarbonyl, aryl-C₁₋₆alkylaminocarbonyl, aryl-C₂₋₆alkenylaminocarbonyl, aryl-C₂₋₆alkynylaminocarbonyl, N-aryl-N-cyclo C₃₋₇alkylaminocarbonyl, heteroarylaminocarbonyl, diheteroarylaminocarbonyl, heteroaryl-C₁₋₆alkylaminocarbonyl, heteroaryl-C₂₋₆alkenylaminocarbonyl, heteroaryl-C₂₋₆alkynylaminocarbonyl, N-heteroaryl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-heteroaryl-N-arylaminocarbonyl, heterocyclylaminocarbonyl, diheterocyclylaminocarbonyl, heterocyclyl-C₁₋₆alkylaminocarbonyl, heterocyclyl-C₂₋₆alkenylaminocarbonyl, heterocyclyl-C₂₋₆alkynylaminocarbonyl, N-heterocyclyl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-heterocyclyl-N-arylaminocarbonyl, N-heterocyclyl-Nheteroarylaminocarbonyl, C₁₋₆alkylsulfinyl, cycloC₃₋₁₂alkylsulfinyl, C₂₋₆alkenylsulfinyl, C₂₋₆alkynylsulfinyl, arylsulfinyl, heteroarylsulfinyl, heterocyclylsulfinyl, C₁₋₆alkylsulfonyl, cycloC₃₋₁₂alkylsulfonyl, C₂₋₆alkenylsulfonyl, C₂₋₆alkynylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heterocyclylsulfonyl, C₁₋₆alkylsulfonylamino, or arylsulfonylamino and

R¹¹ represents hydrogen, C₁₋₆alkyl, cycloC₃₋₁₂alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, acyl, aryl, heteroaryl, heterocyclyl, C₁₋₆alkylaminocarbonyl, di-C₁₋₆alkylaminocarbonyl, C₁₋₆alkylsulfonyl, arylsulfonyl or heteroarylsulfonyl;

Y¹, Y², Y³, and Y⁴ represent C or N, wherein at least two of Y¹, Y², Y³, and Y⁴ represent C;

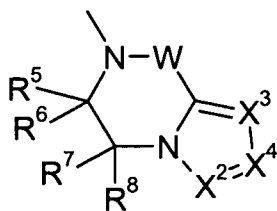
R^{12} and R^{13} , which may be the same or different, each independently represent hydrogen, halogen, amino, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, aryl, C_{1-6} alkyl, cyclo C_{3-12} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, cyclo C_{3-12} alkyloxy, C_{2-6} alkenyloxy, C_{2-6} alkynyloxy, heteroaryl, heterocyclyl, aryloxy, heteroaryloxy, heterocyclyloxy, C_{1-6} alkylamino, di- C_{1-6} alkylamino, cyclo C_{3-12} alkylamino, di-cyclo C_{3-12} alkylamino, N- C_{1-6} alkyl-N-cyclo C_{3-12} alkylamino, C_{2-6} alkenylamino, C_{2-6} alkynylamino, di- C_{2-6} alkenylamino, di- C_{2-6} alkynylamino, N- C_{1-6} alkyl-N- C_{2-6} alkenylamino, N- C_{1-6} alkyl-N- C_{2-6} alkynylamino, N- C_{2-6} alkenyl-N-cyclo C_{3-12} alkylamino, N- C_{2-6} alkynyl-N-cyclo C_{3-12} alkylamino, N- C_{2-6} alkenyl-N- C_{2-6} alkynylamino, arylamino, diarylamino, aryl- C_{1-6} alkylamino, aryl- C_{2-6} alkenylamino, aryl- C_{2-6} alkynylamino, N-aryl-N-cyclo C_{3-12} alkylamino, heteroarylamino, diheteroarylamino, heteroaryl- C_{1-6} alkylamino, heteroaryl- C_{2-6} alkenylamino, heteroaryl- C_{2-6} alkynylamino, N-heteroaryl-N-cyclo C_{3-12} alkylamino, N-heteroaryl-N-arylamino, heterocyclylamino, diheterocyclylamino, heterocyclyl- C_{1-6} alkylamino, heterocyclyl- C_{2-6} alkenylamino, heterocyclyl- C_{2-6} alkynylamino, N-heterocyclyl-N-cyclo C_{3-12} alkylamino, N-heterocyclyl-N-arylamino, N-heterocyclyl-N-heteroarylamino, acyl, acyloxy, acylamino, C_{1-6} alkoxycarbonyl, cyclo C_{3-12} alkoxycarbonyl, C_{2-6} alkenyloxycarbonyl, C_{2-6} alkynyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, heterocyclyloxycarbonyl, aminocarbonyl, C_{1-6} alkylaminocarbonyl, di- C_{1-6} alkylaminocarbonyl, cyclo C_{3-12} alkylaminocarbonyl, di-cyclo C_{3-12} alkylaminocarbonyl, N- C_{1-6} alkyl-N-cyclo C_{3-12} alkylaminocarbonyl, C_{2-6} alkenylaminocarbonyl, C_{2-6} alkynylaminocarbonyl, di- C_{2-6} alkenylaminocarbonyl, di- C_{2-6} alkynylaminocarbonyl, N- C_{1-6} alkyl-N- C_{2-6} alkenylaminocarbonyl, N- C_{1-6} alkyl-N- C_{2-6} alkynylaminocarbonyl, N- C_{2-6} alkenyl-N-cyclo C_{3-12} alkylaminocarbonyl, N- C_{2-6} alkynyl-N-cyclo C_{3-12} alkylaminocarbonyl, N- C_{2-6} alkenyl-N- C_{2-6} alkynylaminocarbonyl, arylaminocarbonyl, diarylamino, aryl- C_{1-6} alkylaminocarbonyl, aryl- C_{2-6} alkenylaminocarbonyl, aryl- C_{2-6} alkynylaminocarbonyl, N-aryl-N-cyclo C_{3-7} alkylaminocarbonyl, heteroarylamino, diheteroarylamino, heteroaryl- C_{1-6} alkylaminocarbonyl, heteroaryl- C_{2-6} alkenylaminocarbonyl, heteroaryl- C_{2-6} alkynylaminocarbonyl, N-heteroaryl-

N-cycloC₃₋₁₂alkylaminocarbonyl, N-heteroaryl-N-arylaminocarbonyl, heterocyclylaminocarbonyl, diheterocyclylaminocarbonyl, heterocyclyl-C₁₋₆alkylaminocarbonyl, heterocyclyl-C₂₋₆alkenylaminocarbonyl, heterocyclyl-C₂₋₆alkynylaminocarbonyl, N-heterocyclyl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-heterocyclyl-N-arylaminocarbonyl, N-heterocyclyl-N-heteroarylaminocarbonyl, C₁₋₆alkylsulfinyl, cycloC₃₋₁₂alkylsulfinyl, C₂₋₆alkenylsulfinyl, C₂₋₆alkynylsulfinyl, arylsulfinyl, heteroarylsulfinyl, heterocyclylsulfinyl, C₁₋₆alkylsulfonyl, cycloC₃₋₁₂alkylsulfonyl, C₂₋₆alkenylsulfonyl, C₂₋₆alkynylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heterocyclylsulfonyl, C₁₋₆alkylsulfonylamino, or arylsulfonylamino;

or R¹² and R¹³ together with the two carbon atoms carrying them represent an aryl group which may be optionally substituted by a group selected from halogen, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl, and C₁₋₆alkoxy; a heteroaryl group having 5 or 6 ring members which may be optionally substituted by a group selected from halogen, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl, and C₁₋₆alkoxy; or a heterocyclyl group having 5 or 6 ring members, which may be optionally substituted by a group selected from oxo, halogen, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl, and C₁₋₆alkoxy;

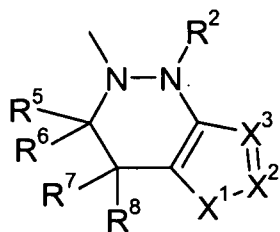
and optical isomers, pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof.

2. A compound as claimed in Claim 1, wherein A represents



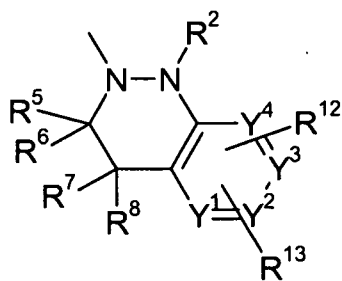
wherein R⁵, R⁶, R⁷, and R⁸, which may be the same or different, each independently represent hydrogen or C₁₋₆alkyl, and X², X³, and X⁴, which may be the same or different represent CR⁹ or N.

3. A compound as claimed in Claim 2, wherein W represents CR^3R^4 , and R^3 and R^4 , which may be the same or different, each independently represent hydrogen or C_{1-6} alkyl, and R^9 represents hydrogen, halogen, cyano, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylaminocarbonyl, cyclo C_{3-12} alkylaminocarbonyl, aryl or heteroaryl.
4. A compound as claimed in Claim 3, wherein R^3 and R^4 , which may be the same or different, each independently represent hydrogen or methyl, and R^9 represents hydrogen, halogen, cyano, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylaminocarbonyl, cyclo C_{3-12} alkylaminocarbonyl or a heteroaryl group selected from tetrazolyl, furyl, thienyl, pyridinyl, pyrimidinyl, and pyrazinyl, wherein the heteroaryl group may be optionally substituted by one or more groups selected from halogen and C_{1-6} alkyl.
5. A compound as claimed in Claim 2, wherein W represents NR^2 , and R^2 represents hydrogen or C_{1-6} alkyl, and R^9 represents hydrogen, halogen, cyano, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylaminocarbonyl, cyclo C_{3-12} alkylaminocarbonyl, aryl or heteroaryl.
6. A compound as claimed in Claim 5, wherein R^2 represents hydrogen or methyl.
7. A compound as claimed in Claim 1, wherein A represents



wherein R^2 , R^5 , R^6 , R^7 , and R^8 , which may be the same or different, each independently represent hydrogen or C_{1-6} alkyl.

8. A compound as claimed in Claim 7, wherein X^1 represents NR^{11} , wherein R^{11} represents hydrogen or C_{1-6} alkyl, S, or O and X^2 and X^3 represent CR^9 .
9. A compound as claimed in Claim 8, wherein R^9 represents hydrogen, halogen, or C_{1-6} alkyl.
10. A compound as claimed in Claim 1, wherein A represents



wherein R^2 , R^5 , R^6 , R^7 , and R^8 , which may be the same or different, each independently represent hydrogen or C_{1-6} alkyl.

11. A compound as claimed in Claim 10, wherein R^2 , R^5 , R^6 , R^7 , and R^8 , which may be the same or different, each independently represent hydrogen or methyl.
12. A compound as claimed in Claim 11, wherein R^{12} and R^{13} , which may be the same or different, each independently represent hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylsulphonyl, trifluoromethyl, aryl, heteroaryl, or C_{1-6} alkylcarbonylamino.
13. A compound as claimed in Claim 12, wherein one of R^{12} and R^{13} represents hydrogen and the other represents hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylsulphonyl, trifluoromethyl, aryl, heteroaryl, or C_{1-6} alkylcarbonylamino.
14. A compound as defined in claim 1 for the prevention and/or treatment of a condition or disease associated with abnormal glutamate neurotransmission, or a method for modulating mGluR5 receptors to achieve therapeutic benefit.

15. A compound as claimed in Claim 14, wherein the condition associated with abnormal glutamate transmission, or wherein modulation of mGluR5 receptors results in therapeutic benefit is selected from: Alzheimer's disease, Creutzfeld-Jakob's syndrome/disease, bovine spongiform encephalopathy (BSE), prion related infections, diseases involving mitochondrial dysfunction, diseases involving β -amyloid and/or tauopathy, Down's syndrome, hepatic encephalopathy, Huntington's disease, motor neuron diseases, amyotrophic lateral sclerosis (ALS), olivoponto-cerebellar atrophy, post-operative cognitive deficit (POCD), systemic lupus erythematosus, systemic sclerosis, Sjogren's syndrome, Neuronal Ceroid Lipofuscinosis, neurodegenerative cerebellar ataxias, Parkinson's disease, Parkinson's dementia, mild cognitive impairment, cognitive deficits in various forms of mild cognitive impairment, cognitive deficits in various forms of dementia, dementia pugilistica, vascular and frontal lobe dementia, cognitive impairment, learning impairment, eye injuries, eye diseases, eye disorders, glaucoma, retinopathy, macular degeneration, head or brain or spinal cord injuries, head or brain or spinal cord trauma, trauma, hypoglycaemia, hypoxia, perinatal hypoxia, ischaemia, ischaemia resulting from cardiac arrest or stroke or bypass operations or transplants, convulsions, epileptic convulsions, epilepsy, temporal lobe epilepsy, myoclonic epilepsy, inner ear insult, inner ear insult in tinnitus, tinnitus, sound- or drug-induced inner ear insult, sound- or drug-induced tinnitus, L-dopa-induced dyskinesias, L-dopa-induced dyskinesias in Parkinson's disease therapy, dyskinesias, dyskinesia in Huntington's disease, drug induced dyskinesias, neuroleptic-induced dyskinesias, haloperidol-induced dyskinesias, dopaminomimetic-induced dyskinesias, chorea, Huntington's chorea, athetosis, dystonia, stereotypy, ballism, tardive dyskinesias, tic disorder, torticollis spasmodicus, blepharospasm, focal and generalized dystonia, nystagmus, hereditary cerebellar ataxias, corticobasal degeneration, tremor, essential tremor, abuse, addiction, nicotine addiction, nicotine abuse, alcohol addiction, alcohol abuse, opiate addiction, opiate abuse, cocaine addiction, cocaine abuse, amphetamine addiction, amphetamine abuse, anxiety disorders, panic

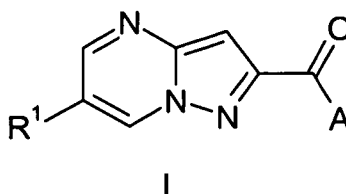
disorders, anxiety and panic disorders, social anxiety disorder (SAD), attention deficit hyperactivity disorder (ADHD), attention deficit syndrome (ADS), restless leg syndrome (RLS), hyperactivity in children, autism, dementia, dementia in Alzheimer's disease, dementia in Korsakoff syndrome, Korsakoff syndrome, vascular dementia, dementia related to HIV infections, HIV-1 encephalopathy, AIDS encephalopathy, AIDS dementia complex, AIDS-related dementia, major depressive disorder, major depression, depression, depression resulting from Borna virus infection, major depression resulting from Borna virus infection, bipolar manic-depressive disorder, drug tolerance, drug tolerance to opioids, movement disorders, fragile-X syndrome, irritable bowel syndrome (IBS), migraine, multiple sclerosis (MS), muscle spasms, pain, chronic pain, acute pain, inflammatory pain, neuropathic pain, diabetic neuropathic pain (DNP), pain related to rheumatic arthritis, allodynia, hyperalgesia, nociceptive pain, cancer pain, posttraumatic stress disorder (PTSD), schizophrenia, positive or cognitive or negative symptoms of schizophrenia, spasticity, Tourette's syndrome, urinary incontinence, vomiting, pruritic conditions, pruritis, sleep disorders, micturition disorders, neuromuscular disorder in the lower urinary tract, gastroesophageal reflux disease (GERD), gastrointestinal dysfunction, lower esophageal sphincter (LES) disease, functional gastrointestinal disorders, dyspepsia, regurgitation, respiratory tract infection, bulimia nervosa, chronic laryngitis, asthma, reflux-related asthma, lung disease, eating disorders, obesity, obesity-related disorders, obesity abuse, food addiction, binge eating disorders, agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, social phobia, phobic disorders, substance-induced anxiety disorder, delusional disorder, schizoaffective disorder, schizophreniform disorder, substance-induced psychotic disorder, or delirium; inhibition of tumour cell growth, migration, invasion, adhesion and toxicity in the peripheral tissues, peripheral nervous system and CNS; neoplasia, hyperplasia, dysplasia, cancer, carcinoma, sarcoma, oral cancer, squamous cell carcinoma (SCC), oral squamous cell carcinoma (SCC), lung cancer, lung adenocarcinoma, breast cancer, prostate cancer, gastric cancer, liver cancer, colon cancer,

colorectal carcinoma, rhabdomyosarcoma, brain tumour, tumour of a nerve tissue, glioma, malignant glioma, astroglioma, neuroglioma, neuroblastoma, glioblastoma, medulloblastoma, cancer of skin cells, melanoma, malignant melanoma, epithelial neoplasm, lymphoma, myeloma, Hodgkin's disease, Burkitt's lymphoma, leukemia, thymoma, tumours, diabetes, hyperammonemia, liver failure and sleep disturbances.

16. A compound as claimed in Claim 14, wherein the condition associated with abnormal glutamate transmission, or wherein modulation of mGluR5 receptors results in therapeutic benefit is selected from: chronic pain, neuropathic pain, diabetic neuropathic pain (DNP), cancer pain, pain related to rheumatic arthritis, inflammatory pain, L-dopa-induced dyskinesias, dopaminomimetic-induced dyskinesias, L-dopa-induced dyskinesias in Parkinson's disease therapy, dopaminomimetic-induced dyskinesias in Parkinson's disease therapy, tardive dyskinesias, Parkinson's disease, anxiety disorders, panic disorders, anxiety and panic disorders, social anxiety disorder (SAD), generalized anxiety disorder, substance-induced anxiety disorder, eating disorders, obesity, binge eating disorders, Huntington's chorea, epilepsy, Alzheimer's disease, positive and negative symptoms of schizophrenia, cognitive impairment, functional gastrointestinal disorders, gastroesophageal reflux disease (GERD), migraine, irritable bowel syndrome (IBS), cognitive enhancement and neuroprotection.
17. A compound as claimed in Claim 14, wherein the condition associated with abnormal glutamate transmission, or wherein modulation of mGluR5 receptors results in therapeutic benefit is selected from: chronic pain, neuropathic pain, diabetic neuropathic pain (DNP), cancer pain, pain related to rheumatic arthritis, inflammatory pain, L-dopa-induced dyskinesias, dopaminomimetic-induced dyskinesias, L-dopa-induced dyskinesias in Parkinson's disease therapy, dopaminomimetic-induced dyskinesias in Parkinson's disease therapy, tardive dyskinesias, Parkinson's disease, anxiety disorders, panic disorders, anxiety and panic disorders, social anxiety disorder (SAD), generalized anxiety disorder, substance-induced anxiety

disorder, eating disorders, obesity, binge eating disorders, migraine, irritable bowel syndrome (IBS), functional gastrointestinal disorders, gastroesophageal reflux disease (GERD), Huntington's chorea and epilepsy.

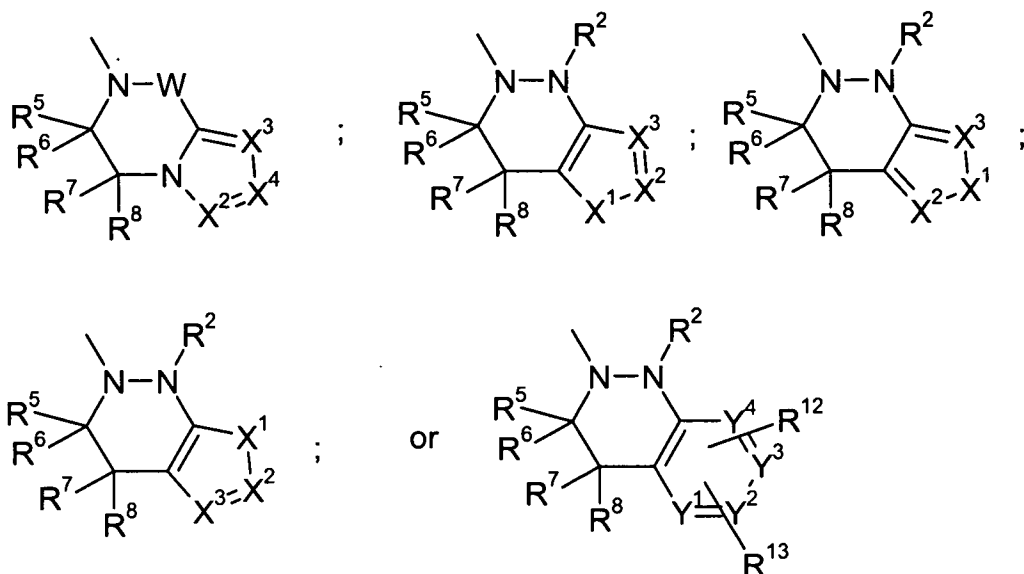
18. A compound as claimed in Claim 14, wherein the condition associated with abnormal glutamate transmission, or wherein modulation of mGluR5 receptors results in therapeutic benefit is selected from: Alzheimer's disease, positive and/or negative symptoms of schizophrenia, cognitive impairment, cognitive enhancement and neuroprotection.
19. A compound as claimed in Claim 14, wherein the condition associated with abnormal glutamate transmission, or wherein modulation of mGluR5 receptors results in therapeutic benefit, is a binge eating disorder.
20. Use of a compound as defined in Claim 1 for the manufacture of a medicament for treating or preventing a condition or disease associated with abnormal glutamate neurotransmission, or for modulating mGluR5 receptors to achieve therapeutic benefit.
21. A pharmaceutical composition comprising as active ingredient at least one compound of Claim 1, together with one or more pharmaceutically acceptable excipients.
22. A pharmaceutical composition comprising a combination of at least one compound of Claim 1 and at least one NMDA receptor antagonist, together with one or more pharmaceutically acceptable excipients.
23. A process for the synthesis of a compound selected from those of Formula I



wherein

R^1 represents chloro or bromo;

A represents



wherein

W represents NR^2 or CR^3R^4

R^2 represents hydrogen, C_{1-6} alkyl, trifluoromethyl or cyclo C_{3-12} alkyl;

R^3 , R^4 , R^5 , R^6 , which may be the same or different, each independently represent hydrogen, C_{1-6} alkyl, cyclo C_{3-12} alkyl, or trifluoromethyl;

R^7 , and R^8 , which may be the same or different, each independently represent hydrogen, C_{1-6} alkyl, cyclo C_{3-12} alkyl, amino, hydroxy, halogen, or trifluoromethyl;

X^1 represents CR^9R^{10} , NR^{11} , S, or O, and X^2 , X^3 , and X^4 , which may be the same or different each independently represent CR^9 or N, wherein

R^9 and R^{10} , which may be the same or different, each independently represent hydrogen, halogen, amino, hydroxy, nitro, cyano,

trifluoromethyl, trifluoromethoxy, aryl, C₁₋₆alkyl, cycloC₃₋₁₂alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, cycloC₃₋₁₂alkyloxy, C₂₋₆alkenyloxy, C₂₋₆alkynyloxy, heteroaryl, heterocyclyl, aryloxy, heteroaryloxy, heterocyclyloxy, C₁₋₆alkylamino, di-C₁₋₆alkylamino, cycloC₃₋₁₂alkylamino, di-cycloC₃₋₁₂alkylamino, N-C₁₋₆alkyl-N-cycloC₃₋₁₂alkylamino, C₂₋₆alkenylamino, C₂₋₆alkynylamino, di-C₂₋₆alkenylamino, di-C₂₋₆alkynylamino, N-C₁₋₆alkyl-N-C₂₋₆alkenylamino, N-C₁₋₆alkyl-N-C₂₋₆alkynylamino, N-C₂₋₆alkenyl-N-cycloC₃₋₁₂alkylamino, N-C₂₋₆alkynyl-N-cycloC₃₋₁₂alkylamino, N-C₂₋₆alkenyl-N-C₂₋₆alkynylamino, arylamino, diarylamino, aryl-C₁₋₆alkylamino, aryl-C₂₋₆alkenylamino, aryl-C₂₋₆alkynylamino, N-aryl-N-cycloC₃₋₁₂alkylamino, heteroarylamino, diheteroarylamino, heteroaryl-C₁₋₆alkylamino, heteroaryl-C₂₋₆alkenylamino, heteroaryl-C₂₋₆alkynylamino, N-heteroaryl-N-cycloC₃₋₁₂alkylamino, N-heteroaryl-N-arylamino, heterocyclylamino, diheterocyclylamino, heterocyclyl-C₁₋₆alkylamino, heterocyclyl-C₂₋₆alkenylamino, heterocyclyl-C₂₋₆alkynylamino, N-heterocyclyl-N-cycloC₃₋₁₂alkylamino, N-heterocyclyl-N-arylamino, N-heterocyclyl-N-heteroarylamino, acyl, acyloxy, acylamino, C₁₋₆alkoxycarbonyl, cycloC₃₋₁₂alkoxycarbonyl, C₂₋₆alkenyloxy carbonyl, C₂₋₆alkynyloxy carbonyl, aryloxy carbonyl, heteroaryloxy carbonyl, heterocyclyloxy carbonyl, aminocarbonyl, C₁₋₆alkylaminocarbonyl, di-C₁₋₆alkylaminocarbonyl, cycloC₃₋₁₂alkylaminocarbonyl, di-cycloC₃₋₁₂alkylaminocarbonyl, N-C₁₋₆alkyl-N-cycloC₃₋₁₂alkylaminocarbonyl, C₂₋₆alkenylaminocarbonyl, C₂₋₆alkynylaminocarbonyl, di-C₂₋₆alkenylaminocarbonyl, di-C₂₋₆alkynylaminocarbonyl, N-C₁₋₆alkyl-N-C₂₋₆alkenylaminocarbonyl, N-C₁₋₆alkyl-N-C₂₋₆alkynylaminocarbonyl, N-C₂₋₆alkenyl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-C₂₋₆alkynyl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-C₂₋₆alkenyl-N-C₂₋₆alkynylaminocarbonyl, arylaminocarbonyl, diarylamino carbonyl, aryl-C₁₋₆alkylaminocarbonyl, aryl-C₂₋₆alkenylaminocarbonyl, aryl-C₂₋₆alkynylaminocarbonyl, N-aryl-N-cyclo C₃₋₇alkylaminocarbonyl,

heteroarylaminocarbonyl, diheteroarylaminocarbonyl, heteroaryl-C₁₋₆alkylaminocarbonyl, heteroaryl-C₂₋₆alkenylaminocarbonyl, heteroaryl-C₂₋₆alkynylaminocarbonyl, N-heteroaryl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-heteroaryl-N-arylaminocarbonyl, heterocyclylaminocarbonyl, diheterocyclylaminocarbonyl, heterocyclyl-C₁₋₆alkylaminocarbonyl, heterocyclyl-C₂₋₆alkenylaminocarbonyl, heterocyclyl-C₂₋₆alkynylaminocarbonyl, N-heterocyclyl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-heterocyclyl-N-arylaminocarbonyl, N-heterocyclyl-Nheteroarylaminocarbonyl, C₁₋₆alkylsulfinyl, cycloC₃₋₁₂alkylsulfinyl, C₂₋₆alkenylsulfinyl, C₂₋₆alkynylsulfinyl, arylsulfinyl, heteroarylsulfinyl, heterocyclylsulfinyl, C₁₋₆alkylsulfonyl, cycloC₃₋₁₂alkylsulfonyl, C₂₋₆alkenylsulfonyl, C₂₋₆alkynylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heterocyclylsulfonyl, C₁₋₆alkylsulfonylamino, or arylsulfonylamino and

R¹¹ represents hydrogen, C₁₋₆alkyl, cycloC₃₋₁₂alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, acyl, aryl, heteroaryl, heterocyclyl, C₁₋₆alkylaminocarbonyl, di-C₁₋₆alkylaminocarbonyl, C₁₋₆alkylsulfonyl, arylsulfonyl or heteroarylsulfonyl;

Y¹, Y², Y³, and Y⁴ represent C or N, wherein at least two of Y¹, Y², Y³, and Y⁴ represent C;

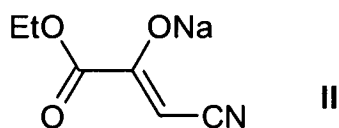
R¹² and R¹³, which may be the same or different, each independently represent hydrogen, halogen, amino, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, aryl, C₁₋₆alkyl, cycloC₃₋₁₂alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, cycloC₃₋₁₂alkyloxy, C₂₋₆alkenyloxy, C₂₋₆alkynyloxy, heteroaryl, heterocyclyl, aryloxy, heteroaryloxy, heterocycliloxy, C₁₋₆alkylamino, di-C₁₋₆alkylamino, cycloC₃₋₁₂alkylamino, di-cycloC₃₋₁₂alkylamino, N-C₁₋₆alkyl-N-cycloC₃₋₁₂alkylamino, C₂₋₆alkenylamino, C₂₋₆alkynylamino, di-C₂₋₆alkenylamino, di-C₂₋₆alkynylamino, N-C₁₋₆alkyl-N-C₂₋₆alkenylamino, N-C₁₋₆alkyl-N-C₂₋₆alkynylamino, N-C₂₋₆alkenyl-N-cycloC₃₋₁₂alkylamino, N-C₂₋

alkynyl-N-cycloC₃₋₁₂alkylamino, N-C₂₋₆alkenyl-N-C₂₋₆alkynylamino
 arylamino, diarylamino, aryl-C₁₋₆alkylamino, aryl-C₂₋₆alkenylamino, aryl-C₂₋₆
 alkynylamino, N-aryl-N-cycloC₃₋₁₂alkylamino, heteroarylamino,
 diheteroarylamino, heteroaryl-C₁₋₆alkylamino, heteroaryl-C₂₋₆alkenylamino,
 heteroaryl-C₂₋₆alkynylamino, N-heteroaryl-N-cycloC₃₋₁₂alkylamino, N-
 heteroaryl-N-arylamino, heterocyclylamino, diheterocyclylamino,
 heterocyclyl-C₁₋₆alkylamino, heterocyclyl-C₂₋₆alkenylamino, heterocyclyl-
 C₂₋₆alkynylamino, N-heterocyclyl-N-cycloC₃₋₁₂alkylamino, N-heterocyclyl-
 N-arylamino, N-heterocyclyl-N-heteroarylamino, acyl, acyloxy, acylamino,
 C₁₋₆alkoxycarbonyl, cycloC₃₋₁₂alkoxycarbonyl, C₂₋₆alkenyloxycarbonyl, C₂₋₆
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 heterocyclyxycarbonyl, aminocarbonyl, C₁₋₆alkylaminocarbonyl, di-C₁₋₆
 alkylaminocarbonyl, cycloC₃₋₁₂alkylaminocarbonyl, di-cycloC₃₋₁₂
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 arylaminocarbonyl, diarylamino, aryl-C₁₋₆alkylaminocarbonyl, aryl-
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 C₃₋₇alkylaminocarbonyl, heteroarylamino, dihetero-
 arylaminocarbonyl, heteroaryl-C₁₋₆alkylaminocarbonyl, heteroaryl-C₂₋₆
 alkenylaminocarbonyl, heteroaryl-C₂₋₆alkynylaminocarbonyl, N-heteroaryl-
 N-cycloC₃₋₁₂alkylaminocarbonyl, N-heteroaryl-N-arylamino, N-heteroaryl-
 heterocyclylaminocarbonyl, diheterocyclylaminocarbonyl, heterocyclyl-C₁₋₆
 alkylaminocarbonyl, heterocyclyl-C₂₋₆alkenylaminocarbonyl, heterocyclyl-
 C₂₋₆alkynylaminocarbonyl, N-heterocyclyl-N-cycloC₃₋₁₂alkylaminocarbonyl,
 N-heterocyclyl-N-arylamino, N-heterocyclyl-N-
 heteroarylamino, C₁₋₆alkylsulfinyl, cycloC₃₋₁₂alkylsulfinyl, C₂₋₆
 alkenylsulfinyl, C₂₋₆alkynylsulfinyl, arylsulfinyl, heteroarylsulfinyl,
 heterocyclylsulfinyl, C₁₋₆alkylsulfonyl, cycloC₃₋₁₂alkylsulfonyl, C₂₋₆

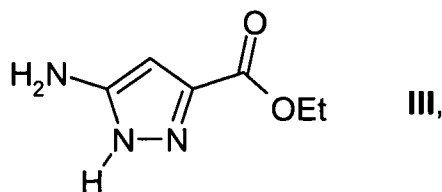
alkenylsulfonyl, C₂₋₆alkynylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heterocyclysulfonyl, C₁₋₆alkylsulfonylamino, or arylsulfonylamino;

or R¹² and R¹³ together with the two carbon atoms carrying them represent an aryl group which may be optionally substituted by a group selected from halogen, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl, and C₁₋₆alkoxy; a heteroaryl group having 5 or 6 ring members which may be optionally substituted by a group selected from halogen, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl, and C₁₋₆alkoxy; or a heterocyclyl group having 5 or 6 ring members, which may be optionally substituted by a group selected from oxo, halogen, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl, and C₁₋₆alkoxy;

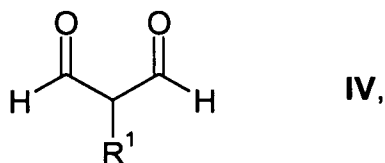
and optical isomers, pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof, wherein a compound of Formula II



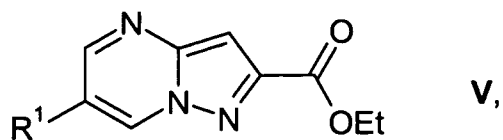
is suspended in a mixture of ethanol and water and treated with hydrochloric acid, followed by reaction with H₂NNHCOOCH₃ to yield a compound of Formula III



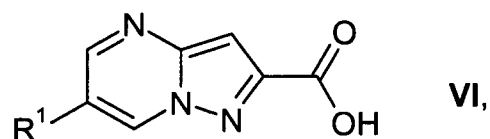
which is reacted with a compound of Formula IV



to yield a compound of Formula V



which is hydrolyzed under acidic conditions to yield a compound of Formula **VI**

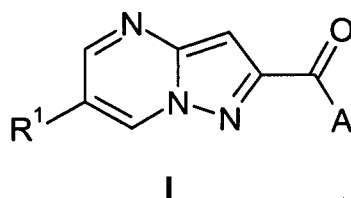


which is treated with an amine of Formula **VII**



in the presence of a condensing agent, to yield a compound of Formula **I**, which is converted, if desired, to a pharmaceutically acceptable salt, hydrate, solvate, or polymorph.

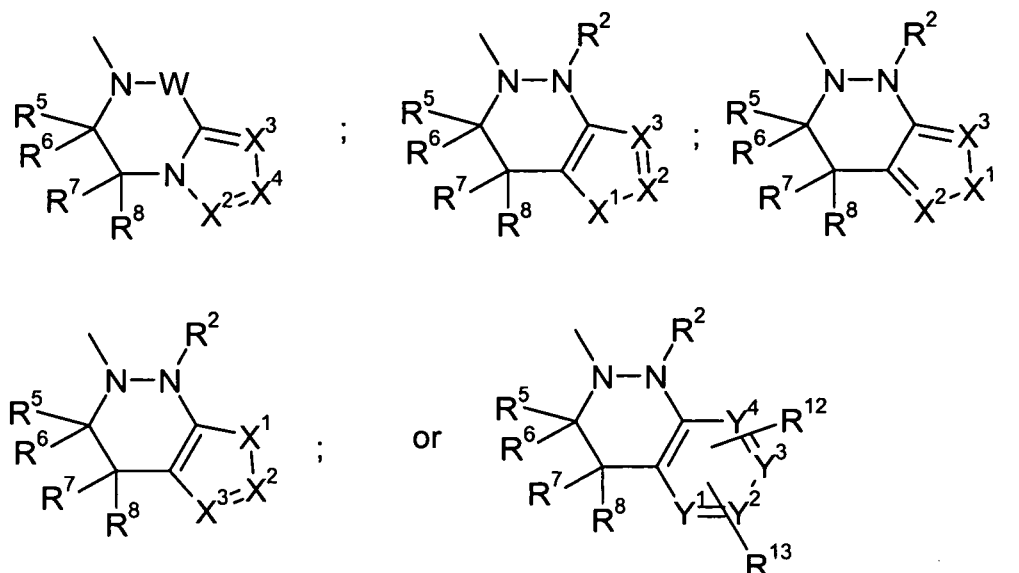
24. A process for the synthesis of a compound selected from those of Formula **I**



wherein

R^1 represents chloro or bromo;

A represents



wherein

W represents NR^2 or CR^3R^4

R^2 represents hydrogen, C_{1-6} alkyl, trifluoromethyl or cyclo C_{3-12} alkyl;

R^3 , R^4 , R^5 , R^6 , which may be the same or different, each independently represent hydrogen, C_{1-6} alkyl, cyclo C_{3-12} alkyl, or trifluoromethyl;

R^7 , and R^8 , which may be the same or different, each independently represent hydrogen, C_{1-6} alkyl, cyclo C_{3-12} alkyl, amino, hydroxy, halogen, or trifluoromethyl;

X^1 represents CR^9R^{10} , NR^{11} , S, or O, and X^2 , X^3 , and X^4 , which may be the same or different each independently represent CR^9 or N, wherein

R^9 and R^{10} , which may be the same or different, each independently represent hydrogen, halogen, amino, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, aryl, C_{1-6} alkyl, cyclo C_{3-12} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, cyclo C_{3-12} alkyloxy, C_{2-6} alkenyloxy, C_{2-6} alkynyloxy, heteroaryl, heterocyclyl, aryloxy, heteroaryloxy, heterocyclyloxy, C_{1-6} alkylamino, di- C_{1-6} alkylamino, cyclo C_{3-12} alkylamino, di-cyclo C_{3-12} alkylamino, N- C_{1-6} alkyl-N-cyclo C_{3-12} alkylamino,

₁₂alkylamino, C₂₋₆alkenylamino, C₂₋₆alkynylamino, di-C₂₋₆alkenylamino, di-C₂₋₆alkynylamino, N-C₁₋₆alkyl-N-C₂₋₆alkenylamino, N-C₁₋₆alkyl-N-C₂₋₆alkynylamino, N-C₂₋₆alkenyl-N-cycloC₃₋₁₂alkylamino, N-C₂₋₆alkynyl-N-cycloC₃₋₁₂alkylamino, N-C₂₋₆alkenyl-N-C₂₋₆alkynylamino arylamino, diarylamino, aryl-C₁₋₆alkylamino, aryl-C₂₋₆alkenylamino, aryl-C₂₋₆alkynylamino, N-aryl-N-cycloC₃₋₁₂alkylamino, heteroarylamino, diheteroarylamino, heteroaryl-C₁₋₆alkylamino, heteroaryl-C₂₋₆alkenylamino, heteroaryl-C₂₋₆alkynylamino, N-heteroaryl-N-cycloC₃₋₁₂alkylamino, N-heteroaryl-N-arylamino, heterocyclylamino, diheterocyclylamino, heterocyclyl-C₁₋₆alkylamino, heterocyclyl-C₂₋₆alkenylamino, heterocyclyl-C₂₋₆alkynylamino, N-heterocyclyl-N-cycloC₃₋₁₂alkylamino, N-heterocyclyl-N-arylamino, N-heterocyclyl-N-heteroarylamino, acyl, acyloxy, acylamino, C₁₋₆alkoxycarbonyl, cycloC₃₋₁₂alkoxycarbonyl, C₂₋₆alkenyloxycarbonyl, C₂₋₆alkynyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, heterocyclilyloxycarbonyl, aminocarbonyl, C₁₋₆alkylaminocarbonyl, di-C₁₋₆alkylaminocarbonyl, cycloC₃₋₁₂alkylaminocarbonyl, di-cycloC₃₋₁₂alkylaminocarbonyl, N-C₁₋₆alkyl-N-cycloC₃₋₁₂alkylaminocarbonyl, C₂₋₆alkenylaminocarbonyl, C₂₋₆alkynylaminocarbonyl, di-C₂₋₆alkenylaminocarbonyl, di-C₂₋₆alkynylaminocarbonyl, N-C₁₋₆alkyl-N-C₂₋₆alkenylaminocarbonyl, N-C₁₋₆alkyl-N-C₂₋₆alkynylaminocarbonyl, N-C₂₋₆alkenyl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-C₂₋₆alkynyl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-C₂₋₆alkenyl-N-C₂₋₆alkynylaminocarbonyl, arylaminocarbonyl, diarylamino, aryl-C₁₋₆alkylaminocarbonyl, aryl-C₂₋₆alkenylaminocarbonyl, aryl-C₂₋₆alkynylaminocarbonyl, N-aryl-N-cyclo C₃₋₇alkylaminocarbonyl, heteroarylaminocarbonyl, diheteroarylaminocarbonyl, heteroaryl-C₁₋₆alkylaminocarbonyl, heteroaryl-C₂₋₆alkenylaminocarbonyl, heteroaryl-C₂₋₆alkynylaminocarbonyl, N-heteroaryl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-heteroaryl-N-arylaminocarbonyl, heterocyclylaminocarbonyl, diheterocyclylaminocarbonyl,

heterocyclyl-C₁₋₆alkylaminocarbonyl, heterocyclyl-C₂₋₆alkenylaminocarbonyl, heterocyclyl-C₂₋₆alkynylaminocarbonyl, N-heterocyclyl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-heterocyclyl-N-arylamino carbonyl, N-heterocyclyl-Nheteroarylamino carbonyl, C₁₋₆alkylsulfinyl, cycloC₃₋₁₂alkylsulfinyl, C₂₋₆alkenylsulfinyl, C₂₋₆alkynylsulfinyl, arylsulfinyl, heteroarylsulfinyl, heterocyclylsulfinyl, C₁₋₆alkylsulfonyl, cycloC₃₋₁₂alkylsulfonyl, C₂₋₆alkenylsulfonyl, C₂₋₆alkynylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heterocyclylsulfonyl, C₁₋₆alkylsulfonylamino, or arylsulfonylamino and

R¹¹ represents hydrogen, C₁₋₆alkyl, cycloC₃₋₁₂alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, acyl, aryl, heteroaryl, heterocyclyl, C₁₋₆alkylaminocarbonyl, di-C₁₋₆alkylaminocarbonyl, C₁₋₆alkylsulfonyl, arylsulfonyl or heteroarylsulfonyl;

Y¹, Y², Y³, and Y⁴ represent C or N, wherein at least two of Y¹, Y², Y³, and Y⁴ represent C;

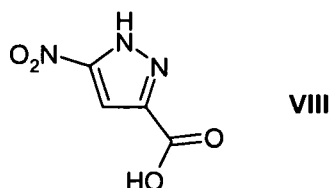
R¹² and R¹³, which may be the same or different, each independently represent hydrogen, halogen, amino, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, aryl, C₁₋₆alkyl, cycloC₃₋₁₂alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, cycloC₃₋₁₂alkyloxy, C₂₋₆alkenyloxy, C₂₋₆alkynyloxy, heteroaryl, heterocyclyl, aryloxy, heteroaryloxy, heterocyclioxy, C₁₋₆alkylamino, di-C₁₋₆alkylamino, cycloC₃₋₁₂alkylamino, di-cycloC₃₋₁₂alkylamino, N-C₁₋₆alkyl-N-cycloC₃₋₁₂alkylamino, C₂₋₆alkenylamino, C₂₋₆alkynylamino, di-C₂₋₆alkenylamino, di-C₂₋₆alkynylamino, N-C₁₋₆alkyl-N-C₂₋₆alkenylamino, N-C₁₋₆alkyl-N-C₂₋₆alkynylamino, N-C₂₋₆alkenyl-N-cycloC₃₋₁₂alkylamino, N-C₂₋₆alkynyl-N-cycloC₃₋₁₂alkylamino, N-C₂₋₆alkenyl-N-C₂₋₆alkynylamino, arylamino, diarylamino, aryl-C₁₋₆alkylamino, aryl-C₂₋₆alkenylamino, aryl-C₂₋₆alkynylamino, N-aryl-N-cycloC₃₋₁₂alkylamino, heteroarylamino, diheteroarylamino, heteroaryl-C₁₋₆alkylamino, heteroaryl-C₂₋₆alkenylamino, heteroaryl-C₂₋₆alkynylamino, N-heteroaryl-N-cycloC₃₋₁₂alkylamino, N-

heteroaryl-N-arylamino, heterocyclylamino, diheterocyclylamino, heterocyclyl-C₁₋₆alkylamino, heterocyclyl-C₂₋₆alkenylamino, heterocyclyl-C₂₋₆alkynylamino, N-heterocyclyl-N-cycloC₃₋₁₂alkylamino, N-heterocyclyl-N-arylamino, N-heterocyclyl-N-heteroarylamino, acyl, acyloxy, acylamino, C₁₋₆alkoxycarbonyl, cycloC₃₋₁₂alkoxycarbonyl, C₂₋₆alkenylloxycarbonyl, C₂₋₆alkynylloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, heterocyclylloxycarbonyl, aminocarbonyl, C₁₋₆alkylaminocarbonyl, di-C₁₋₆alkylaminocarbonyl, cycloC₃₋₁₂alkylaminocarbonyl, di-cycloC₃₋₁₂alkylaminocarbonyl, N-C₁₋₆alkyl-N-cycloC₃₋₁₂alkylaminocarbonyl, C₂₋₆alkenylaminocarbonyl, C₂₋₆alkynylaminocarbonyl, di-C₂₋₆alkenylaminocarbonyl, di-C₂₋₆alkynylaminocarbonyl, N-C₁₋₆alkyl-N-C₂₋₆alkenylaminocarbonyl, N-C₁₋₆alkyl-N-C₂₋₆alkynylaminocarbonyl, N-C₂₋₆alkenyl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-C₂₋₆alkynyl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-C₂₋₆alkenyl-N-C₂₋₆alkynylaminocarbonyl, arylaminocarbonyl, diarylamino carbonyl, aryl-C₁₋₆alkylaminocarbonyl, aryl-C₂₋₆alkenylaminocarbonyl, aryl-C₂₋₆alkynylaminocarbonyl, N-aryl-N-cycloC₃₋₇alkylaminocarbonyl, heteroarylamino carbonyl, diheteroarylamino carbonyl, heteroaryl-C₁₋₆alkylaminocarbonyl, heteroaryl-C₂₋₆alkenylaminocarbonyl, heteroaryl-C₂₋₆alkynylaminocarbonyl, N-heteroaryl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-heteroaryl-N-arylamino carbonyl, heterocyclylaminocarbonyl, diheterocyclylaminocarbonyl, heterocyclyl-C₁₋₆alkylaminocarbonyl, heterocyclyl-C₂₋₆alkenylaminocarbonyl, heterocyclyl-C₂₋₆alkynylaminocarbonyl, N-heterocyclyl-N-cycloC₃₋₁₂alkylaminocarbonyl, N-heterocyclyl-N-arylamino carbonyl, N-heterocyclyl-N-heteroarylamino carbonyl, C₁₋₆alkylsulfinyl, cycloC₃₋₁₂alkylsulfinyl, C₂₋₆alkenylsulfinyl, C₂₋₆alkynylsulfinyl, arylsulfinyl, heteroarylsulfinyl, heterocyclylsulfinyl, C₁₋₆alkylsulfonyl, cycloC₃₋₁₂alkylsulfonyl, C₂₋₆alkenylsulfonyl, C₂₋₆alkynylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heterocyclylsulfonyl, C₁₋₆alkylsulfonylamino, or arylsulfonylamino;

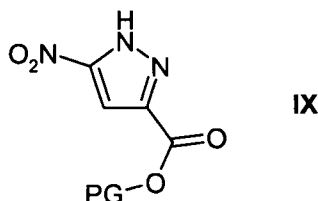
or R¹² and R¹³ together with the two carbon atoms carrying them represent an aryl group which may be optionally substituted by a group selected from halogen, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl,

and C₁₋₆alkoxy; a heteroaryl group having 5 or 6 ring members which may be optionally substituted by a group selected from halogen, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl, and C₁₋₆alkoxy; or a heterocyclyl group having 5 or 6 ring members, which may be optionally substituted by a group selected from oxo, halogen, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl, and C₁₋₆alkoxy;

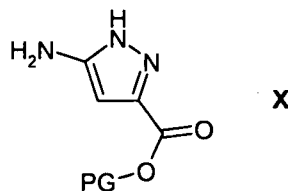
and optical isomers, pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof, wherein a compound of Formula VIII



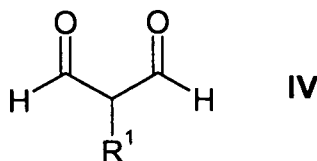
is dissolved in an alcoholic solvent and treated with thionyl chloride to yield a compound of Formula IX



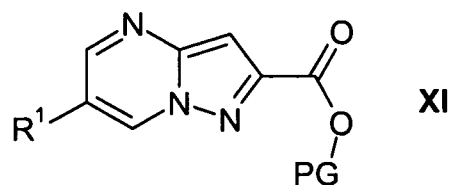
wherein PG represents C₁₋₆alkyl, which is reduced under standard conditions to yield a compound of Formula X



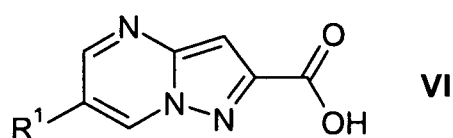
which is reacted with a compound of Formula IV



to yield a compound of Formula **XI**



which is hydrolyzed under acidic conditions to yield a compound of Formula **VI**



which is treated with an amine of Formula **VII**



in the presence of a condensing agent, to yield a compound of Formula **I**, which is converted, if desired, to a pharmaceutically acceptable salt, hydrate, solvate, or polymorph.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2009/000616

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D487/04 C07D519/00 A61K31/519 A61P25/00 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/039439 A (HOFFMANN LA ROCHE [CH]; GATTI MCARTHUR SILVIA [CH]; GOETSCHI ERWIN [CH] 12 April 2007 (2007-04-12) claim 2; examples	1-24
A	WO 2006/084634 A (HOFFMANN LA ROCHE [CH]; GATTI MCARTHUR SILVIA [CH]; GOETSCHI ERWIN [CH] 17 August 2006 (2006-08-17) claims	1-24



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

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- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

17 April 2009

Date of mailing of the international search report

27/04/2009

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Authorized officer

Bosma, Peter

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2009/000616

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		US 2006183756 A1	17-08-2006