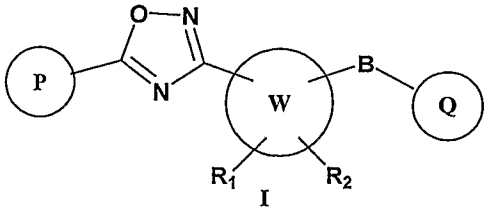
# SUBSTITUTED OXADIAZOLE DERIVATIVES AS POSITIVE ALLOSTERIC MODULATORS OF METABOTROPIC GLUTAMATE RECEPTORS

## FIELD OF THE INVENTION




I

The present invention provides new compounds of formula I as positive allosteric modulators of metabotropic receptors – subtype 5 ("mGluR5") which are useful for the treatment or prevention of central nervous system disorders such as for example: cognitive decline, both positive and negative symptoms in schizophrenia as well as various other central or peripheral nervous system disorders in which the mGluR5 subtype of glutamate metabotropic receptor is involved. The invention is also directed to pharmaceutical compounds and compositions in the prevention or treatment of such diseases in which mGluR5 is involved.

## BACKGROUND OF THE INVENTION

Glutamate, the major amino-acid transmitter in the mammalian central nervous system (CNS), mediates excitatory synaptic neurotransmission through the activation of ionotropic glutamate receptors receptor-channels (iGluRs, namely NMDA, AMPA and kainate) and metabotropic glutamate receptors (mGluRs). iGluRs are responsible for fast excitatory transmission (Nakanishi S et al., (1998) Brain Res. Rev., 26:230-235) while mGluRs have a more modulatory role that contributes to the fine-tuning of synaptic efficacy. Glutamate performs numerous physiological functions such as long-term potentiation (LTP), a process believed to underlie learning and memory but also cardiovascular regulation, sensory perception, and the development of synaptic plasticity. In addition, glutamate plays an important role in the patho-physiology of different neurological and psychiatric diseases, especially when an imbalance in glutamatergic neurotransmission occurs.

The mGluRs are seven-transmembrane G protein-coupled receptors. The eight members of the family are classified into three groups (Groups I, II & III) according to their sequence homology and pharmacological properties (Schoepp DD et al. (1999) Neuropharmacology, 38:1431-1476). Activation of mGluRs lead to a large variety of intracellular responses and activation of different transductional cascades. Among mGluR members, the mGluR5 subtype is of high interest for counterbalancing the deficit or excesses of neurotransmission in neuropsychatric diseases. mGluR5 belongs to Group I and its activation initiates cellular responses through G-protein mediated mechanisms. mGluR5 is coupled to phospholipase C and stimulates phosphoinositide hydrolysis and intracellular calcium mobilization.

mGluR5 proteins have been demonstrated to be localized in post-synaptic elements adjacent to the post-synaptic density (Lujan R et al. (1996) Eur. J. Neurosci., 8:1488-

500; Lujan R et al. (1997) J. Chem. Neuroanat., 13:219-41) and are rarely detected in the pre-synaptic elements (Romano C et al. (1995) J. Comp. Neurol., 355:455-69). mGluR5 receptors can therefore modify the post-synaptic responses to neurotransmitter or regulate neurotransmitter release.

In the CNS, mGluR5 receptors are abundant mainly throughout the cortex, hippocampus, caudate-putamen and nucleus accumbens. As these brain areas have been shown to be involved in emotion, motivational processes and in numerous aspects of cognitive function, mGluR5 modulators are predicted to be of therapeutic interest.

A variety of potential clinical indications have been suggested to be targets for the development of subtype selective mGluR modulators. These include epilepsy, neuropathic and inflammatory pain, numerous psychiatric disorders (eg anxiety and schizophrenia), movement disorders (eg Parkinson disease), neuroprotection (stroke and head injury), migraine and addiction/drug dependency (for reviews, see Brauner-Osborne H et al. (2000) J. Med. Chem., 43:2609-45; Bordi F and Ugolini A. (1999) Prog. Neurobiol., 59:55-79; Spooren W et al. (2003) Behav. Pharmacol., 14:257-77).

The hypothesis of hypofunction of the glutamatergic system as reflected by NMDA receptor hypofunction as a putative cause of schizophrenia has received increasing support over the past few years (Goff DC and Coyle JT (2001) Am. J. Psychiatry, 158:1367-1377; Carlsson A et al. (2001) Annu. Rev. Pharmacol. Toxicol., 41:237-260 for a review). Evidence implicating dysfunction of glutamatergic neurotransmission is supported by the finding that antagonists of the NMDA subtype of glutamate receptor can reproduce the full range of symptoms as well as the physiologic manifestation of schizophrenia such as hypofrontality, impaired prepulse inhibition and enhanced subcortical dopamine release. In addition, clinical studies have suggested that mGluR5 allele frequency is associated with schizophrenia among certain cohorts (Devon RS et al. (2001) Mol. Psychiatry., 6:311-4) and that an increase in mGluR5 message has been found in cortical pyramidal cells layers of schizophrenic brain (Ohnuma T et al. (1998) Brain Res. Mol. Brain Res., 56:207-17).

The involvement of mGluR5 in neurological and psychiatric disorders is supported by evidence showing that in vivo activation of group I mGluRs induces a potentiation of NMDA receptor function in a variety of brain regions mainly through the activation of mGluR5 receptors (Mannaioni G et al. (2001) Neurosci., 21:5925-34; Awad H et al. (2000) J. Neurosci., 20:7871-7879; Pisani A et al. (2001) Neuroscience, 106:579-87; Benquet P et al (2002) J. Neurosci., 22:9679-86).

The role of glutamate in memory processes also has been firmly established during the past decade (Martin SJ et al. (2000) Annu. Rev. Neurosci., 23:649-711; Baudry M and Lynch G. (2001) Neurobiol. Learn. Mem., 76:284-297). The use of mGluR5 null mutant mice have strongly supported a role of mGluR5 in learning and memory. These mice show a selective loss in two tasks of spatial learning and memory, and reduced CA1 LTP (Lu et al. (1997) J. Neurosci., 17:5196-5205; Schulz B et al. (2001) Neuropharmacology, 41:1-7; Jia Z et al. (2001) Physiol. Behav., 73:793-802; Rodrigues et al. (2002) J. Neurosci., 22:5219-5229).

The finding that mGluR5 is responsible for the potentiation of NMDA receptor mediated currents raises the possibility that agonists of this receptor could be useful as cognitive-enhancing agents, but also as novel antipsychotic agents that act by selectively enhancing NMDA receptor function.

The activation of NMDARs could potentiate hypofunctional NMDARs in neuronal circuitry relevant to schizophrenia. Recent in vivo data strongly suggest that mGluR5 activation may be a novel and efficacious approach to treat cognitive decline and both positive and negative symptoms in schizophrenia (Kinney GG et al. (2003) J. Pharmacol. Exp. Ther., 306(1):116-123).

mGluR5 receptor is therefore being considered as a potential drug target for treatment of psychiatric and neurological disorders including treatable diseases in this connection are anxiety disorders, attentional disorders, eating disorders, mood disorders, psychotic disorders, cognitive disorders, personality disorders and substance-related disorders.

Most of the current modulators of mGluR5 function have been developed as structural analogues of glutamate, quisqualate or phenylglycine (Schoepp DD et al. (1999) Neuropharmacology, 38:1431-1476) and it has been very challenging to develop in vivo active and selective mGluR5 modulators acting at the glutamate binding site. A new avenue for developing selective modulators is to identify molecules that act through allosteric mechanisms, modulating the receptor by binding to site different from the highly conserved orthosteric binding site.

Positive allosteric modulators of mGluRs have emerged recently as novel pharmacological entities offering this attractive alternative. This type of molecule has been discovered for mGluR1, mGluR2, mGluR4, and mGluR5 (Knoflach F et al. (2001) Proc. Natl. Acad. Sci. U S A., 98:13402-13407; O'Brien JA et al. (2003) Mol. Pharmacol., 64:731-40 ; Johnson K et al. (2002) Neuropharmacology, 43:291; Johnson MP et al. (2003) J. Med. Chem., 46:3189-92; Marino MJ et al. (2003) Proc. Natl. Acad. Sci. U S A., 100(23):13668-73; for a review see Mutel V (2002) Expert Opin. Ther. Patents, 12:1-8; Kew JN (2004) Pharmacol. Ther., 104(3):233-44; Johnson MP et al. (2004) Biochem. Soc. Trans., 32:881-7). DFB and related molecules were described as in vitro mGluR5 positive allosteric modulators but with low potency (O'Brien JA et al. (2003) Mol. Pharmacol., 64:731-40). Benzamide derivatives have been patented (WO 2004/087048; O'Brien JA (2004) J. Pharmacol. Exp. Ther., 309:568-77) and recently aminopyrazole derivatives have been disclosed as mGluR5 positive allosteric modulators (Lindsley et al. (2004) J. Med. Chem., 47:5825-8; WO 2005/087048). Among aminopyrazole derivatives, CDPPB has shown in vivo activity antipsychotic-like effects in rat behavioral models (Kinney GG et al. (2005) J. Pharmacol. Exp. Ther., 313:199-206). This report is consistent with the hypothesis that allosteric potentiation of mGluR5 may provide a novel approach for development of antipsychotic agents. Recently a novel series of positive allosteric modulators of mGluR5 receptors has been disclosed (WO 2005/044797).
Aryloxadiazole derivatives have been disclosed (WO 04/014902 and WO 04/014370) ; these compounds are negative allosteric modulators of mGluR5 receptors. International publication N° WO 04/054973 describes aryloxyoxadiazoles as histamine H3 receptor antagonist. Another class of 2-piperidinyl aryloxadiazole is

disclosed in WO 99/45006; these derivatives are rotamase enzyme inhibitors. Cyclopropyloxadiazoles compounds are been disclosed in US 3966748.

None of the specifically disclosed compounds are structurally related to the compounds of the present invention.

The present invention relates to a method of treating or preventing a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of mGluR5 positive allosteric modulators.

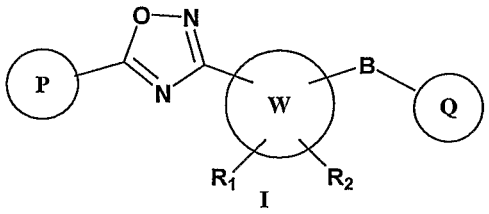
FIGURES

Figure 1 shows the effect of 10 μM of example #1 of the present invention on primary cortical mGluR5-expressing cell cultures in the absence or in the presence of 300nM glutamate.

Figure 2 shows that the representative compound # 1 of the invention significantly attenuated the increase in locomotor activity induced by amphetamine at doses of 30 mg/kg ip.

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, there are provided new compounds of the general formula I




I

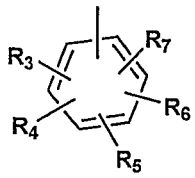
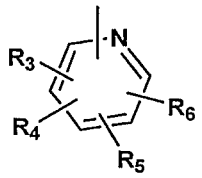
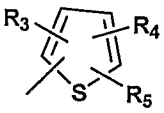
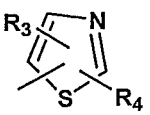
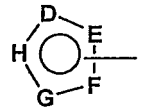
Or pharmaceutically acceptable salts, hydrates or solvates of such compounds

Wherein

W represents ($C_5$-$C_7$)cycloalkyl, ($C_3$-$C_7$)heterocycloalkyl, ($C_3$-$C_7$)heterocycloalkyl-($C_1$-$C_3$)alkyl or ($C_3$-$C_7$)heterocycloalkenyl ring;

$R_1$ and $R_2$ represent independently hydrogen, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, arylalkyl, heteroarylalkyl, hydroxy, amino, aminoalkyl, hydroxyalkyl, -($C_1$-$C_6$)alkoxy or $R_1$ and $R_2$ together can form a ($C_3$-$C_7$)cycloalkyl ring, a carbonyl bond C=O or a carbon double bond;

P and Q are each independently selected and denote a cycloalkyl, a heterocycloalkyl, an aryl or heteroaryl group of formula

$R_3$, $R_4$, $R_5$, $R_6$, and $R_7$ independently are hydrogen, halogen, $-NO_2$, $-(C_1-C_6)$alkyl, $-(C_3-C_6)$cycloalkyl, $-(C_3-C_7)$cycloalkylalkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, halo-$(C_1-C_6)$alkyl, heteroaryl, heteroarylalkyl, arylalkyl, aryl, $-OR_8$, $-NR_8R_9$, $-C(=NR_{10})NR_8R_9$, $-NR_8COR_9$, $NR_8CO_2R_9$, $NR_8SO_2R_9$, $-NR_{10}CO\ NR_8R_9$, $-SR_8$, $-S(=O)R_8$, $-S(=O)_2R_8$, $-S(=O)_2NR_8R_9$, $-C(=O)R_8$, $-C(=O)-O-R_8$, $-C(=O)NR_8R_9$, $-C(=NR_8)R_9$, or $C(=NOR_8)R_9$ substituents; wherein optionally two substituents are combined to the intervening atoms to form a bicyclic heterocycloalkyl, aryl or heteroaryl ring; wherein each ring is optionally further substituted with 1-5 independent halogen, -CN, $-(C_1-C_6)$alkyl, $-O-(C_0-C_6)$alkyl, $-O-(C_3-C_7)$cycloalkylalkyl, -O(aryl), -O(heteroaryl), $-O-(-C_1-C_3)$alkylaryl, $-O-(C_1-C_3)$alkylheteroaryl, $-N((-C_0-C_6)$alkyl$)((C_0-C_3)$alkylaryl) or $-N((C_0-C_6)$alkyl$)((C_0-C_3-)$alkylheteroaryl) groups;

$R_8$, $R_9$, $R_{10}$ each independently is hydrogen, $(C_1-C_6)$alkyl, $(C_3-C_6)$cycloalkyl, $(C_3-C_7)$cycloalkylalkyl, $(C_2-C_6)$alkenyl, $(C_2-C_6)$alkynyl, halo-$(C_1-C_6)$alkyl, heterocycloalkyl, heteroaryl, heteroarylalkyl, arylalkyl or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, $-(C_1-C_6)$alkyl, $-O-(C_0-C_6)$alkyl, $-O-(C_3-C_7)$cycloalkylalkyl, -O(aryl), -O(heteroaryl), $-N(C_0-C_6$-alkyl$)_2$,$-N((C_0-C_6)$alkyl$)((C_3-C_7-)$cycloalkyl) or $-N((C_0-C_6)$alkyl$)$(aryl) substituents;

D, E, F, G and H represent independently $-C(R_3)=$, $-C(R_3)=C(R_4)-$,$-C(=O)-$,$-C(=S)-$, $-O-$, $-N=$, $-N(R_3)-$ or $-S-$;

B represents a single bond, $-C(=O)-(C_0-C_2)$alkyl-, $-C(=O)-(C_2-C_6)$alkenyl-, $-C(=O)-(C_2-C_6)$alkynyl-, $-C(=O)-O-$, $-C(=O)NR_8-(C_0-C_2)$alkyl-, $-C(=NR_8)NR_9-S(=O)-(C_0-C_2)$alkyl-, $-S(=O)_2-(C_0-C_2)$alkyl-, $-S(=O)_2NR_8-(C_0-C_2)$alkyl-, $C(=NR_8)-(C_0-C_2)$alkyl-, $-C(=NOR_8)-(C_0-C_2)$alkyl- or $-C(=NOR_8)NR_9-(C_0-C_2)$alkyl-;

$R_8$ and $R_9$, independently are as defined above;

Any N may be an N-oxide;

The present invention includes both possible stereoisomers and includes not only racemic compounds but the individual enantiomers as well.

For the avoidance of doubt it is to be understood that in this specification "$(C_1-C_6)$" means a carbon group having 1, 2, 3, 4, 5 or 6 carbon atoms. "$(C_0-C_6)$" means a carbon group having 0, 1, 2, 3, 4, 5 or 6 carbon atoms.
In this specification "C" means a carbon atom.

In the above definition, the term "($C_1$-$C_6$)alkyl" includes group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, hexyl or the like.

"($C_2$-$C_6$)alkenyl" includes group such as ethenyl, 1-propenyl, allyl, isopropenyl, 1-butenyl, 3-butenyl, 4-pentenyl and the like.

"($C_2$-$C_6$)alkynyl" includes group such as ethynyl, propynyl, butynyl, pentynyl and the like.

"Halogen" includes atoms such as fluorine, chlorine, bromine and iodine.

"Cycloalkyl" refers to an optionally substituted carbocycle containing no heteroatoms, includes mono-, bi-, and tricyclic saturated carbocycles, as well as fused ring systems. Such fused ring systems can include on ring that is partially or fully unsaturated such as a benzene ring to form fused ring systems such as benzo fused carbocycles. Cycloalkyl includes such fused ring systems as spirofused ring systems. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decahydronaphthalene, adamantane, indanyl, fluorenyl, 1,2,3,4-tetrahydronaphthalene and the like.

"Heterocycloalkyl" refers to an optionally substituted carbocycle containing at least one heteroatom selected independently from O, N, S. It includes mono-, bi-, and tricyclic saturated carbocycles, as well as fused ring systems. Such fused ring systems can include one ring that is partially or fully unsaturated such as a benzene ring to form fused ring systems such as benzo fused carbocycles. Examples of heterocycloalkyl include piperidine, piperazine, morpholine, tetrahydrothiophene, indoline, isoquinoline and the like.

"Aryl" includes ($C_6$-$C_{10}$)aryl group such as phenyl, 1-naphtyl, 2-naphtyl and the like.

"Arylalkyl" includes ($C_6$-$C_{10}$)aryl-($C_1$-$C_3$)alkyl group such as benzyl group, 1-phenylethyl group, 2-phenylethyl group, 1-phenylpropyl group, 2-phenylpropyl group, 3-phenylpropyl group, 1-naphtylmethyl group, 2-naphtylmethyl group or the like.

"Heteroaryl" includes 5-10 membered heterocyclic group containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur to form a ring such as furyl (furan ring), benzofuranyl (benzofuran ring), thienyl (thiophene ring), benzothiophenyl (benzothiophene ring), pyrrolyl (pyrrole ring), imidazolyl (imidazole ring), pyrazolyl (pyrazole ring), thiazolyl (thiazole ring), isothiazolyl (isothiazole ring), triazolyl (triazole ring), tetrazolyl (tetrazole ring), pyridil (pyridine ring), pyrazynyl (pyrazine ring), pyrimidinyl (pyrimidine ring), pyridazinyl (pyridazine ring), indolyl (indole ring), isoindolyl (isoindole ring), benzoimidazolyl (benzimidazole ring), purinyl group (purine ring), quinolyl (quinoline ring), phtalazinyl (phtalazine ring), naphtyridinyl (naphtyridine ring), quinoxalinyl (quinoxaline ring), cinnolyl (cinnoline ring), pteridinyl (pteridine ring), oxazolyl (oxazole ring), isoxazolyl (isoxazole ring), benzoxazolyl (benzoxazole ring), benzothiazolyl (benzothiaziole ring), furazanyl (furazan ring) and the like.

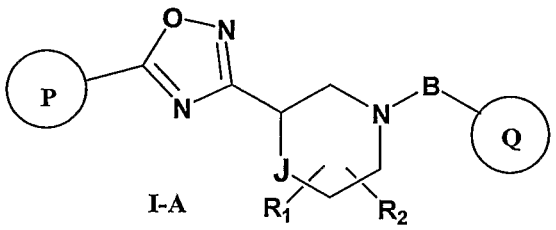
"Heteroarylalkyl" includes heteroaryl-($C_1$-$C_3$-alkyl) group, wherein examples of heteroaryl are the same as those illustrated in the above definition, such as 2-furylmethyl group, 3-furylmethyl group, 2-thienylmethyl group, 3-thienylmethyl group, 1-imidazolylmethyl group, 2-imidazolylmethyl group, 2-thiazolylmethyl group, 2-pyridylmethyl group, 3-pyridylmethyl group, 1-quinolylmethyl group or the like.

"Solvate" refers to a complex of variable stoechiometry formed by a solute (e.g. a compound of formula I) and a solvent. The solvent is a pharmaceutically acceptable solvent as water preferably; such solvent may not interfere with the biological activity of the solute.

"Optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s), which occur, and events that do not occur.

The term "substituted" refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

Preferred compounds of the present invention are compounds of formula I-A depicted below



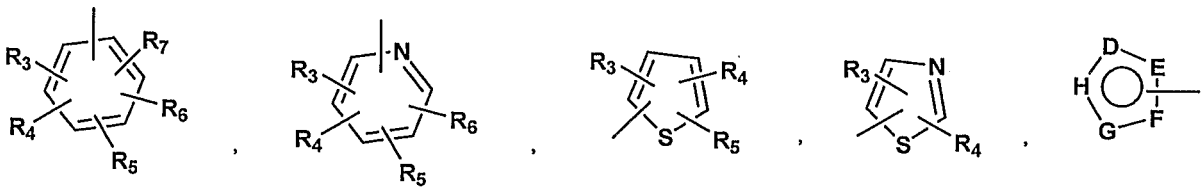

I-A

Or pharmaceutically acceptable salts, hydrates or solvates of such compounds

Wherein

$R_1$ and $R_2$ represent independently hydrogen, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, arylalkyl, heteroarylalkyl, hydroxy, amino, aminoalkyl, hydroxyalkyl, -($C_1$-$C_6$)alkoxy or $R_1$ and $R_2$ together can form a ($C_3$-$C_7$)cycloalkyl ring, a carbonyl bond C=O or a carbon double bond;

P and Q are each independently selected and denote a cycloalkyl, a heterocycloalkyl, an aryl or heteroaryl group of formula




$R_3$, $R_4$, $R_5$, $R_6$, and $R_7$ independently are hydrogen, halogen, -$NO_2$, -($C_1$-$C_6$)alkyl, -($C_3$-$C_6$)cycloalkyl, -($C_3$-$C_7$)cycloalkylalkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, halo-($C_1$-$C_6$)alkyl, heteroaryl,

heteroarylalkyl, arylalkyl, aryl, -$OR_8$, -$NR_8R_9$, -$C(=NR_{10})NR_8R_9$, -$NR_8COR_9$, $NR_8CO_2R_9$, $NR_8SO_2R_9$, -$NR_{10}CO\ NR_8R_9$, -$SR_8$, -$S(=O)R_8$, -$S(=O)_2R_8$, -$S(=O)_2NR_8R_9$, -$C(=O)R_8$, -$C(=O)$-O-$R_8$, -$C(=O)NR_8R_9$, -$C(=NR_8)R_9$, or $C(=NOR_8)R_9$ substituents; wherein optionally two substituents are combined to the intervening atoms to form a bicyclic heterocycloalkyl, aryl or heteroaryl ring; wherein each ring is optionally further substituted with 1-5 independent halogen, -CN, -($C_1$-$C_6$)alkyl, -O-($C_0$-$C_6$)alkyl, -O-($C_3$-$C_7$)cycloalkylalkyl, -O(aryl), -O(heteroaryl), -O-(-$C_1$-$C_3$)alkylaryl, -O-($C_1$-$C_3$)alkylheteroaryl, –N((-$C_0$-$C_6$)alkyl)(($C_0$-$C_3$)alkylaryl) or –N(($C_0$-$C_6$)alkyl)(($C_0$-$C_3$-)alkylheteroaryl) groups;

$R_8$, $R_9$, $R_{10}$ each independently is hydrogen, ($C_1$-$C_6$)alkyl, ($C_3$-$C_6$)cycloalkyl, ($C_3$-$C_7$)cycloalkylalkyl, ($C_2$-$C_6$)alkenyl, ($C_2$-$C_6$)alkynyl, halo-($C_1$-$C_6$)alkyl, heterocycloalkyl, heteroaryl, heteroarylalkyl, arylalkyl or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -($C_1$-$C_6$)alkyl, -O-($C_0$-$C_6$)alkyl, -O-($C_3$-$C_7$)cycloalkylalkyl, -O(aryl), -O(heteroaryl), -N($C_0$-$C_6$-alkyl)$_2$,-N(($C_0$-$C_6$)alkyl)(($C_3$-$C_7$-)cycloalkyl) or –N(($C_0$-$C_6$)alkyl)(aryl) substituents;

D, E, F, G and H represent independently –C($R_3$)=, –C($R_3$)=C($R_4$)-,-C(=O)-,-C(=S)-, –O-, -N=, -N($R_3$)- or -S-;

B represents a single bond, -C(=O)-($C_0$-$C_2$)alkyl-, -C(=O)-($C_2$-$C_6$)alkenyl-, -C(=O)-($C_2$-$C_6$)alkynyl-, -C(=O)-O-, -C(=O)$NR_8$-($C_0$-$C_2$)alkyl-, -C(=$NR_8$)$NR_9$-S(=O)-($C_0$-$C_2$)alkyl-, -S(=O)$_2$-($C_0$-$C_2$)alkyl-, -S(=O)$_2NR_8$-($C_0$-$C_2$)alkyl-, C(=$NR_8$)-($C_0$-$C_2$)alkyl-, -C(=$NOR_8$)-($C_0$-$C_2$)alkyl- or -C(=$NOR_8$)$NR_9$-($C_0$-$C_2$)alkyl-;

$R_8$ and $R_9$, independently are as defined above;

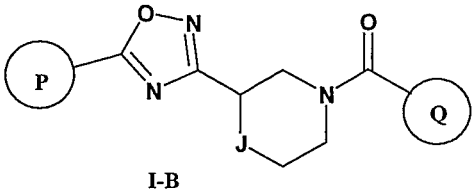
J represents a single bond, –C($R_{11}$)( $R_{12}$), -O-, -N($R_{11}$)- or -S-;

$R_{11}$, $R_{12}$ independently are hydrogen, -($C_1$-$C_6$)alkyl, -($C_3$-$C_6$)cycloalkyl, -($C_3$-$C_7$)cycloalkylalkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, halo($C_1$-$C_6$)alkyl, heteroaryl, heteroarylalkyl, arylalkyl or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -($C_1$-$C_6$)alkyl, -O($C_0$-$C_6$)alkyl, -O($C_3$-$C_7$)cycloalkylalkyl, -O(aryl), -O(heteroaryl), -N(($C_0$-$C_6$)alkyl)(($C_0$-$C_6$)alkyl),-N(($C_0$-$C_6$)alkyl)(($C_3$-$C_7$)cycloalkyl) or –N(($C_0$-$C_6$)alkyl)(aryl) substituents;

Any N may be an N-oxide;

The present invention includes both possible stereoisomers and includes not only racemic compounds but the individual enantiomers as well.

More preferred compounds of the present invention are compounds of formula I-B

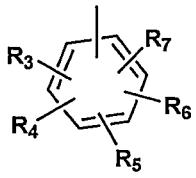
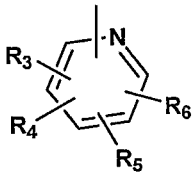
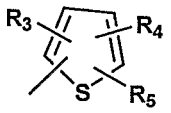
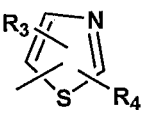
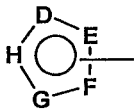


I-B

Or pharmaceutically acceptable salts, hydrates or solvates of such compounds

Wherein

P and Q are each independently selected and denote a cycloalkyl, a heterocycloalkyl, an aryl or heteroaryl group of formula

$R_3$, $R_4$, $R_5$, $R_6$, and $R_7$ independently are hydrogen, halogen, $-NO_2$, $-(C_1-C_6)$alkyl, $-(C_3-C_6)$cycloalkyl, $-(C_3-C_7)$cycloalkylalkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, halo-$(C_1-C_6)$alkyl, heteroaryl, heteroarylalkyl, arylalkyl, aryl, $-OR_8$, $-NR_8R_9$, $-C(=NR_{10})NR_8R_9$, $-NR_8COR_9$, $NR_8CO_2R_9$, $NR_8SO_2R_9$, $-NR_{10}CO\ NR_8R_9$, $-SR_8$, $-S(=O)R_8$, $-S(=O)_2R_8$, $-S(=O)_2NR_8R_9$, $-C(=O)R_8$, $-C(=O)-O-R_8$, $-C(=O)NR_8R_9$, $-C(=NR_8)R_9$, or $C(=NOR_8)R_9$ substituents; wherein optionally two substituents are combined to the intervening atoms to form a bicyclic heterocycloalkyl, aryl or heteroaryl ring; wherein each ring is optionally further substituted with 1-5 independent halogen, -CN, $-(C_1-C_6)$alkyl, $-O-(C_0-C_6)$alkyl, $-O-(C_3-C_7)$cycloalkylalkyl, -O(aryl), -O(heteroaryl), $-O-(-C_1-C_3)$alkylaryl, $-O-(C_1-C_3)$alkylheteroaryl, $-N((-C_0-C_6)$alkyl$)((C_0-C_3)$alkylaryl) or $-N((C_0-C_6)$alkyl$)((C_0-C_3-)$alkylheteroaryl) groups;

$R_8$, $R_9$, $R_{10}$ each independently is hydrogen, $-(C_1-C_6)$alkyl, $-(C_3-C_6)$cycloalkyl, $-(C_3-C_7)$cycloalkylalkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, halo-$(C_1-C_6)$alkyl, heterocycloalkyl, heteroaryl, heteroarylalkyl, arylalkyl or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, $-(C_1-C_6)$alkyl, $-O-(C_0-C_6)$alkyl, $-O-(C_3-C_7)$cycloalkylalkyl, -O(aryl), -O(heteroaryl), $-N(C_0-C_6$-alkyl$)_2$,-$N((C_0-C_6)$alkyl$)((C_3-C_7-)$cycloalkyl) or $-N((C_0-C_6)$alkyl$)$(aryl) substituents;

D, E, F, G and H represent independently $-C(R_3)=$, $-C(R_3)=C(R_4)-$,-C(=O)-,-C(=S)-, –O-, -N=, $-N(R_3)-$ or -S-;

J represents a single bond, $-C(R_{11})(R_{12})$, -O-, $-N(R_{11})-$ or -S-;

$R_{11}$, $R_{12}$ independently are hydrogen, -($C_1$-$C_6$)alkyl, -($C_3$-$C_6$)cycloalkyl, -($C_3$-$C_7$)cycloalkylalkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, halo($C_1$-$C_6$)alkyl, heteroaryl, heteroarylalkyl, arylalkyl or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -($C_1$-$C_6$)alkyl, -O($C_0$-$C_6$)alkyl, -O($C_3$-$C_7$)cycloalkylalkyl, -O(aryl), -O(heteroaryl), -N(($C_0$-$C_6$)alkyl)(($C_0$-$C_6$)alkyl),-N(($C_0$-$C_6$)alkyl)(($C_3$-$C_7$)cycloalkyl) or –N(($C_0$-$C_6$)alkyl)(aryl) substituents;

Any N may be an N-oxide;

The present invention includes both possible stereoisomers and includes not only racemic compounds but the individual enantiomers as well.

Specifically preferred compounds are:

(4-Fluoro-phenyl)-{(S)-3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
(4-Fluoro-phenyl)-{(R)-3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
(3,4-Difluoro-phenyl)-{3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
(2,4-Difluoro-phenyl)-{3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
(4-Fluoro-2-methylamino-phenyl)-{3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
{3-[5-(2-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(5-fluoro-pyridin-2-yl)-methanone
{3-[5-(2-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(5-methyl-isoxazol-4-yl)-methanone
(4-Fluoro-phenyl)-[3-(5-thiazol-4-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
{3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(6-fluoro-pyridin-3-yl)-methanone
(3,4-Difluoro-phenyl)-{3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
(4-Fluoro-phenyl)-[3-(5-pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
(6-Fluoro-pyridin-3-yl)-[3-(5-pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
{3-[5-(2,4-Difluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(4-fluoro-phenyl)-methanone
(4-Fluoro-phenyl)-[3-(5-pyridin-4-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
(3,4-Difluoro-phenyl)-[3-(5-pyridin-4-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
(2,4-Difluoro-phenyl)-[3-(5-pyridin-4-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
(3,4-Difluoro-phenyl)-{3-[5-(2,4-difluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone

(2,4-Difluoro-phenyl)-{3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
(2,4-Difluoro-phenyl)-{3-[5-(2,4-difluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
(5-Methyl-isoxazol-4-yl)-[3-(5-pyridin-4-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
(6-Fluoro-pyridin-3-yl)-[3-(5-pyridin-4-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
(4-Fluoro-2-methyl-phenyl)-[3-(5-pyridin-4-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
(4-Fluoro-2-methyl-phenyl)-{3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
{3-[5-(2,4-Difluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(5-methyl-isoxazol-4-yl)-methanone
{3-[5-(2,4-Difluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(6-fluoro-pyridin-3-yl)-methanone
(4-Fluoro-phenyl)-[3-(5-phenyl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
(4-Fluoro-2-methyl-phenyl)-{3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
{3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(5-methyl-isoxazol-4-yl)-methanone
(6-Fluoro-pyridin-3-yl)-[3-(5-phenyl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
(6-Fluoro-pyridin-3-yl)-[3-(5-thiazol-4-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
{3-[5-(2,4-Difluoro-phenyl)-[1,2,4] oxadiazol-3-yl]-piperidin-1-yl}-(4-fluoro-2-methyl-phenyl)-methanone
(3,4-Difluoro-phenyl)-[3-(5-phenyl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
(2,4-Difluoro-phenyl)-[3-(5-phenyl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
(4-Fluoro-2-methyl-phenyl)-[3-(5-phenyl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
(4-Fluoro-phenyl)-[3-(5-cyclopentyl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
{(S)-3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(6-fluoro-pyridin-3-yl)-methanone
(3,4-Difluoro-phenyl)-{(S)-3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
(3,5-Dimethyl-isoxazol-4-yl)-{(S)-3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
{(S)-3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(5-methyl-isoxazol-4-yl)-methanone
{(S)-3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(2-fluoro-pyridin-4-yl)-methanone
{(S)-3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(3-fluoro-pyridin-4-yl)-methanone
{(S)-3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(5-fluoro-pyridin-2-yl)-methanone
{(S)-3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(5-fluoro-pyridin-3-yl)-methanone

(S)-(4-fluorophenyl)-{3-[5-(5-fluoropyridin-2-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
(S)-(3,4-difluorophenyl)-{3-[5-(5-fluoropyridin-2-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
(S)-(4-fluorophenyl)-{3-[5-(pyridin-2-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
(S)-(3,4-difluorophenyl)-{3-[5-(pyridin-2-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
(4-Fluoro-phenyl)-{(S)-3-[5-(1-methyl-1H-imidazol-4-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
(3,4-Difluoro-phenyl)-{(S)-3-[5-(3-fluoro-pyridin-4-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
(4-Fluoro-phenyl)-{(S)-3-[5-(3-fluoro-pyridin-4-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
[(S)-3-(5-Pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-(2,4,6-trifluoro-phenyl)-methanone
[(S)-3-(5-Pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-(2,3,4-trifluoro-phenyl)-methanone
(2,6-Difluoro-phenyl)-[(S)-3-(5-pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
(2,5-Difluoro-phenyl)-[(S)-3-(5-pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
(2,3-Difluoro-phenyl)-[(S)-3-(5-pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone.

The present invention relates to the pharmaceutically acceptable acid addition salts of compounds of the formula I or pharmaceutically acceptable carriers or excipients.

The present invention relates to a method of treating or preventing a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of mGluR5 allosteric modulators and particularly positive allosteric modulators.

The present invention relates to a method useful for treating or preventing peripheral and central nervous system disorders such as tolerance or dependence, anxiety, depression, psychiatric disease such as psychosis, inflammatory or neuropathic pain, memory impairment, Alzheimer's disease, ischemia, drug abuse and addiction, as defined in the attached claims.

The present invention relates to pharmaceutical compositions which provide from about 0.01 to 1000 mg of the active ingredient per unit dose. The compositions may be administered by any suitable route: for example orally in the form of capsules or tablets, parenterally in the form of solutions for injection, topically in the form of onguents or lotions, ocularly in the form of eye-lotion, rectally in the form of suppositories.

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art; the nature of the pharmaceutical composition employed will depend on the desired route of administration. The total daily dose usually ranges from about 0.05 – 2000 mg.

METHODS OF SYNTHESIS

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

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

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

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

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

The compounds of formula **I** wherein W is a 3-substituted piperidine ring may be prepared according to the synthetic sequence illustrated in Scheme 1.

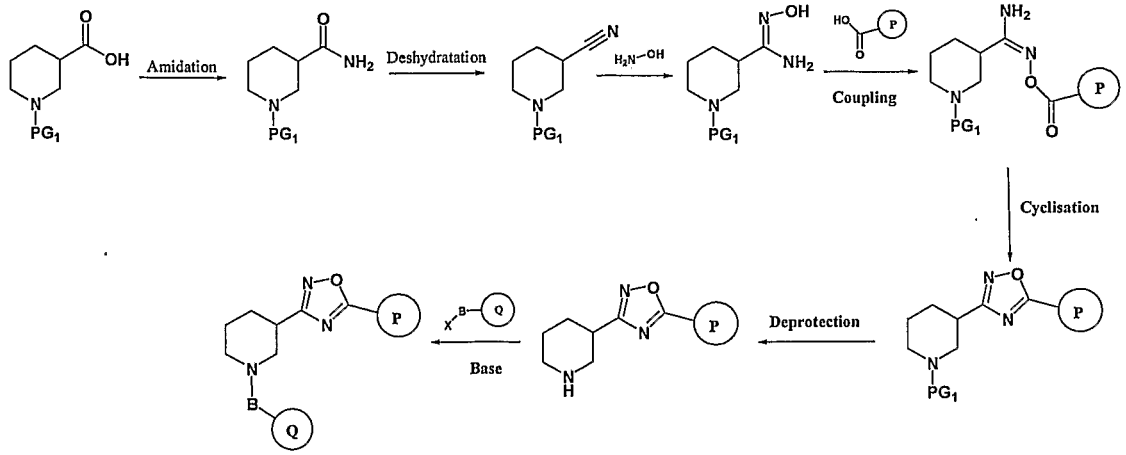
Wherein

P and Q each independently is aryl or heteroaryl as described above

B represents $-C(=O)-(C_0-C_2)$alkyl-; $-S(=O)_2-(C_0-C_2)$alkyl-.

The oxadiazole ring described below is prepared following synthetic routes well known in the art (Katrizky A.R. and Rees C.W. (1984) *Comprehensive Heterocyclic Chemistry*, Pergamon Press).

Scheme 1




The starting nitrile derivative can be prepared in two-steps, starting from the corresponding N-protected nipecotic acid, as outlined in the Scheme 1.
Conversion of N-protected nipecotic acid to the corresponding primary amide can be performed by activating the carboxylic acid with a suitable activating agent and then by reacting it with ammonia. For instance, in a typical procedure the carboxylic acid is dissolved in a suitable solvent (e.g. acetonitrile, chloroform, dichloromethane, tetrahydrofuran, etc.) and a suitable activating agent such as carbonyldiimidazole, ethyl chloroformate, etc. is added at a temperature in the range of 0°C up to room temperature. Sometimes, addition of a suitable organic base such as triethylamine or diisopropylethylamine can be necessary. Then, the reaction mixture is stirred at a temperature in the range of 0°C up to room temperature for a time in the range of 10 minutes up to 1 hour and ammonia (gas) or concentrated aqueous ammonia is added. The reaction typically proceeds at ambient temperature for a time in the range of about 1 hour up to 12 hours.
The primary amide is reacted with a suitable dehydrating agent such as phosphorus oxychloride, thionyl chloride and the like in a suitable solvent (e.g. acetonitrile, pyridine, etc.) or without solvent. Typically the reaction proceeds at a temperature in the range of room temperature up to the refluxing temperature of the solvent, for a time in the range of 3 hours up to 1 night.

The nitrile derivative is reacted with hydroxylamine under neutral or basic conditions such as triethylamine, diisopropyl-ethylamine, sodium carbonate, sodium hydroxide and the like in a suitable solvent *(e.g.* methyl alcohol, ethyl alcohol). The reaction typically proceeds by allowing the reaction temperature to warm slowly from ambient temperature to a temperature range of 70°C up to 80°C inclusive for a time in the range of about 1 hour up to 48 hours inclusive (see for example Lucca, George V. De; Kim, Ui T.; Liang, Jing; Cordova, Beverly; Klabe, Ronald M.; et al; J.Med.Chem.; EN; 41; 13; 1998; 2411-2423, Lila, Christine; Gloanec, Philippe; Cadet, Laurence; Herve, Yolande; Fournier, Jean; et al.; Synth.Commun.; EN; 28; 23; 1998; 4419-4430 and see: Sendzik, Martin; Hui, Hon C.; Tetrahedron Lett.; EN; 44; 2003; 8697-8700 and references therein for reaction under neutral conditions).

The substituted amidoxime derivative may be converted to an acyl-amidoxime derivative using the approach outlined in the Scheme 1. In the Scheme 1, $PG_1$ is an amino protecting group such as *tert*-butyloxycarbonyl, benzyloxycarbonyl, ethoxycarbonyl, benzyl and the like. The coupling reaction may be promoted by

coupling agents known in the art of organic synthesis such as EDCI (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide), DCC (N,N'-dicyclohexyl-carbodiimide), in the presence of a suitable base such as triethylamine, diisopropyl-ethylamine, in a suitable solvent (e.g. tetrahydrofuran, dichloromethane, N,N-dimethylformamide, dioxane). Typically, a co-catalyst such as HOBT (Hydroxy-benzotriazole), HOAT (1-hydroxy-7-azabenzotriazole) may also be present in the reaction mixture. The reaction typically proceeds at a temperature in the range of ambient temperature up to 60°C inclusive for a time in the range of about 2 hours up to 12 hours to produce the intermediate acyl-amidoxime. The cyclisation reaction may be effected thermally in a temperature range of about 80°C up to about 150°C for a time in the range of about 2 hours up to 18 hours (see for example Suzuki, Takeshi; Iwaoka, Kiyoshi; Imanishi, Naoki; Nagakura, Yukinori; Miyata, Keiji; et al.; Chem.Pharm.Bull.; EN; 47; 1; 1999; 120 - 122). . The cyclisation reaction may be effected also by heating under microwaves irradiation in a temperature range of about 80°C up to about 150°C for a time in the range of about 2 hours up to 5 hours. The product from the reaction can be isolated and purified employing standard techniques, such as extraction, chromatography, crystallization, distillation, and the like.

Then, the protecting group $PG_1$ is removed using standard methods. In the Scheme 1, B is as defined above, X is halogen or hydroxyl; for example the piperidine derivative is reacted with an aryl or heteroaryl acyl chloride using methods that are readily apparent to those skilled in the art. The reaction may be promoted by a base such as triethylamine, diisopropylamine, pyridine in a suitable solvent (*e.g.* tetrahydrofuran, dichloromethane). The reaction typically proceeds by allowing the reaction temperature to warm slowly from 0°C up to ambient temperature for a time in the range of about 4 up to 12 hours.
When X is OH, the coupling reaction may be promoted by coupling agents known in the art of organic synthesis such as EDCI (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide), DCC (N,N'-dicyclohexyl-carbodiimide) or by polymer-supported coupling agents such as polymer-supported carbodiimide (PS-DCC, ex Argonaut Technologies), in the presence of a suitable base such as triethylamine, diisopropyl-ethylamine, in a suitable solvent (e.g. tetrahydrofuran, dichloromethane, N,N-dimethylformamide, dioxane). Typically, a co-catalyst such as HOBT (1-Hydroxy-benzotriazole), HOAT (1-hydroxy-7-azabenzotriazole) and the like may also be present in the reaction mixture. The reaction typically proceeds at ambient temperature for a time in the range of about 2 hours up to 12 hours.

The compounds of Formula **I** which are basic in nature can form a wide variety of different pharmaceutically acceptable salts with various inorganic and organic acids. These salts are readily prepared by treating the base compounds with a substantially equivalent amount of the chosen mineral or organic acid in a suitable organic solvent such as methanol, ethanol or isopropanol (see Stahl P.H., Wermuth C.G., *Handbook of Pharmaceuticals Salts, Properties, Selection and Use*, Wiley, 2002).

The following non-limiting examples are intended to illustrate the invention. The physical data given for the compounds exemplified is consistent with the assigned structure of those compounds.

## EXAMPLES

Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification.
Specifically, the following abbreviation may be used in the examples and throughout the specification.

| | |
|---|---|
| g (grams) | rt (room temperature) |
| mg (milligrams) | MeOH (methanol) |
| mL (millilitres) | |
| µl (microliters) | Hz (Hertz) |
| M (molar) | LCMS (Liquid Chromatography Mass Spectrum) |
| MHz (megahertz) | HPLC (High Pressure Liquid Chromatography) |
| mmol (millimoles) | NMR (Nuclear Magnetic Resonance) |
| min (minutes) | 1H (proton) |
| AcOEt (ethyl acetate) | $Na_2SO_4$ (sodium sulphate) |
| $K_2CO_3$ (potassium carbonate) | $MgSO_4$ (magnesium sulphate) |
| $CDCl_3$ (deuteriated chloroform) | HOBT (1-hydroxybenzotriazole) |
| EDCI.HCl (1-3(Dimethylaminopropyl)-3-ethylcarbodiimide, hydrochloride) | RT (Retention Time) |
| EtOH (ethyl alcohol) | NaOH (sodium hydroxide) |
| % (percent) | h (hour) |
| DCM (dichloromethane) | HCl (hydrochloric acid) |
| DIEA (diisopropyl ethyl amine) | n-BuLi (n-butyllithium) |
| Mp (melting point) | THF (tetrahydrofuran) |

All references to brine refer to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions are conducted under an inert atmosphere at room temperature unless otherwise noted.

$^1H$ NMR spectra were recorded on a Brucker 500MHz or on a Brucker 300MHz. Chemical shifts are expressed in parts of million (ppm, δ units). Coupling constants are in units of hertz (Hz) Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quadruplet), q (quintuplet), m (multiplet).

LCMS were recorded under the following conditions:
Method A) Waters Alliance 2795 HT Micromass ZQ. Column Waters XTerra MS C18 (50x4.6 mm, 2.5µm). Flow rate 1 ml/min Mobile phase: A phase = water/$CH_3CN$ 95/5 + 0.05% TFA, B phase = water/$CH_3CN$ = 5/95 + 0.05% TFA. 0-1 min (A: 95%, B: 5%), 1-4 min (A: 0%, B: 100%), 4-6 min (A: 0%, B: 100%), 6-6.1 min (A: 95%, B: 5%). T= 35°C; UV detection: Waters Photodiode array 996, 200-400nm.
Method B) Waters Alliance 2795 HT Micromass ZQ. Column Waters XTerra MS C18 (50x4.6 mm, 2.5µm). Flow rate 1.2 ml/min. Mobile phase: A phase = water/$CH_3CN$ 95/5 + 0.05% TFA, B phase = water/$CH_3CN$ = 5/95 + 0.05% TFA.

0-0.8 min (A: 95%, B: 5%), 0.8-3.3 min (A: 0%, B: 100%), 3.3-5 min (A: 0%, B: 100%), 5-5.1 min (A: 95%, B: 5%). T= 35°C; UV detection: Waters Photodiode array 996, 200-400nm.
Method C) Waters Alliance 2795 HT Micromass ZQ. Column Waters Symmetry C18 (75x4.6 mm, 3.5μm). Flow rate 1 ml/min. Mobile phase: A phase = water/$CH_3CN$ 95/5 + 0.05% TFA, B phase = water/$CH_3CN$ = 5/95 + 0.05% TFA.
0-0.1 min (A: 95%, B: 5%), 1-11 min (A: 0%, B: 100%), 11-12 min (A: 0%, B: 100%), 12-12.1 min (A: 95%, B: 5%). T= 35°C; UV detection: Waters Photodiode array 996, 200-400nm.
Method D) Waters Alliance 2795 HT Micromass ZQ. Column Waters Symmetry C18 (75x4.6 mm, 3.5μm). Flow rate 1.5 ml/min. Mobile phase: A phase = water/$CH_3CN$ 95/5 + 0.05% TFA, B phase = water/$CH_3CN$ = 5/95 + 0.05% TFA.
0-0.5 min (A: 95%, B: 5%), 0.5-7 min (A: 0%, B: 100%), 7-8 min (A: 0%, B: 100%), 8-8.1 min (A: 95%, B: 5%). T= 35°C; UV detection: Waters Photodiode array 996, 200-400nm.
Method E): Pump 515, 2777 Sample Manager, Micromass ZQ Single quadrupole (Waters). Column 2.1*50mm stainless steel packed with 3.5μm SunFire RP C-18 (Waters); flow rate 0.25 ml/min splitting ratio MS :waste/ 1:4; mobile phase: A phase = water/acetonitrile 95/5 + 0.1% TFA, B phase = water/acetonitrile 5/95 + 0.1% TFA. 0-1.0min (A: 98%, B: 2%), 1.0-5.0min (A: 0%, B: 100%), 5.0-9.0min (A: 0%, B: 100%), 9.1-12min (A: 98%, B: 2%); UV detection wavelenght 254 nm; Injection volume: 5μl
Method F) Waters Alliance 2795 HT Micromass ZQ. Column Waters XTerra MS C18 (50x4.6 mm, 2.5μm). Flow rate 1.2 ml/min. Mobile phase: A phase = water/$CH_3CN$ 95/5 + 0.05% TFA, B phase = water/$CH_3CN$ = 5/95 + 0.05% TFA.
0-0.5 min (A: 90%, B: 10%), 0.5-3.5 min (A: 0%, B: 100%), 3.5-5.5 min (A: 0%, B: 100%), 5.5-5.51 min (A: 90%, B: 10%). T= 35°C; UV detection: Waters Photodiode array 996, 200-400nm.
Method G): Pump 1525u (Waters), 2777 Sample Manager, Micromass ZQ2000 Single quadrupole (Waters); PDA detector: 2996 (Waters). Column 2.1*30mm stainless steel packed with 3.0μm Luna C18; flow rate 0.25 ml/min splitting ratio MS :waste/ 1:4; mobile phase: A phase = water/acetonitrile 95/5 + 0.1% TFA, B phase = water/acetonitrile 5/95 + 0.1% TFA. 0-1.5min (A: 98%, B: 2%), 1.0-8.0min (A: 0%, B: 100%), 8.0-11.0min (A: 0%, B: 100%), 11.1-13min (A: 98%, B: 2%); UV detection wavelenght 254 nm; Injection volume: 5μl
Method H): UPLC system Waters Acquity, Micromass ZQ2000 Single quadrupole (Waters). Column 2.1*50mm stainless steel packed with 1.7μm Acquity UPLC-BEH; flow rate 0.40 ml/min; mobile phase: A phase = water/acetonitrile 95/5 + 0.1% TFA, B phase = water/acetonitrile 5/95 + 0.1% TFA. 0-0.25min (A: 98%, B: 2%), 0.25-4.0min (A: 0%, B: 100%), 4.0-5.0min (A: 0%, B: 100%), 5.1-6min (A: 98%, B: 2%); UV detection wavelenght 254 nm.
Method I): HPLC system: Waters Acquity, MS detector: Waters ZQ2000. Column: Acquity UPLC-BEH C18 50x2.1mmx1.7um; flow rate 0.4 ml/min; mobile phase: A phase = water/acetonitrile 95/5 + 0.1% TFA, B phase = water/acetonitrile 5/95 + 0.1% TFA. 0-0.25min (A: 98%, B: 2%), 0.25-4.0min (A: 0%, B: 100%), 4.0-5.0min (A: 0%, B: 100%), 5.1-6min (A: 98%, B: 2%); UV detection wavelenght 254 nm.
Method L): HPLC system: Waters Acquity, MS detector: Waters ZQ2000. Column: Acquity UPLC-BEH C18 50x2.1mmx1.7um; flow rate 0.3 ml/min; mobile phase: A phase = water/acetonitrile 95/5 + 0.1% TFA, B phase = water/acetonitrile 5/95 + 0.1%

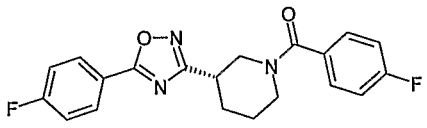
TFA. 0-0.5min (A: 98%, B: 2%), 2.0min (A: 20%, B: 80%), 6.0min (A: 0%, B: 100%), 6.0-9.5min (A: 0%, B: 100%), 9.6min (A: 98%, B: 2%), 9.6-11.0min (A: 98%, B: 2%); UV detection wavelenght 254 nm.
Method M) Waters Alliance 2795 HT Micromass ZQ. Column Waters Symmetry C18 (75x4.6 mm, 3.5µm). Flow rate 1.5 ml/min. Mobile phase: A phase = water/$CH_3CN$ 95/5 + 0.05% TFA, B phase = water/$CH_3CN$ = 5/95 + 0.05% TFA.
0-2 min (A: 95%, B: 5%), 6 min (A: 0%, B: 100%), 6-8 min (A: 0%, B: 100%), 8-8.1 min (A: 95%, B: 5%). T= 35°C; UV detection: Waters Photodiode array 996, 200-400nm.
Method N): UPLC system Waters Acquity, Micromass ZQ2000 Single quadrupole (Waters). Column 2.1*50mm stainless steel packed with 1.7µm Acquity UPLC-BEH; flow rate 0.50 ml/min; mobile phase: A phase = water/acetonitrile 95/5 + 0.05% TFA, B phase = water/acetonitrile 5/95 + 0.05% TFA. 0-0.1min (A: 95%, B: 5%), 1.6min (A: 0%, B: 100%), 1.6-1.9min (A: 0%, B: 100%), 2.4min (A: 95%, B: 5%); UV detection wavelenght 254 nm.

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

Most of the reaction were monitored by thin-layer chromatography on 0.25mm Macherey-Nagel silica gel plates (60F-2254), visualized with UV light. Flash column chromatography was performed on silica gel (220-440 mesh, Fluka).
Melting point determination was performed on a Buchi B-540 apparatus.

Example 1

(4-Fluoro-phenyl)-{(S)-3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone



1 (A) (S)-3-Carbamoyl-piperidine-1-carboxylic acid tert-butyl ester

Triethylamine (1.21mL, 8.72 mmol) and then ethyl chloroformate (0.8 mL, 8.30 mmol) were added dropwise at 0°C to a solution of (S)-1-Boc-piperidine-3-carboxylic acid (2 g, 8.72 mmol) in chloroform (40 mL), under nitrogen atmosphere. After stirring 10 min at 0°C, $NH_3$ (gas) was bubbled into the solution for 1h. The reaction mixture was then stirred at room temperature for 3h, 5% $NaHCO_3$ (aq) was added and the phases were separated. The organic layer was dried over sodium sulphate and evaporated under reduced pressure to afford the title compound, which was used for the next step without further purification.
Yield: quantitative; LCMS (RT): 3.31 min (Method A); MS (ES+) gave m/z: 229.0.

1 (B) (S)-3-Cyano-piperidine-1-carboxylic acid tert-butyl ester

Phosphorus oxychloride (812 uL, 8.72 mmol) was added dropwise at 0°C to a solution of (S)-3-carbamoyl-piperidine-1-carboxylic acid tert-butyl ester (2 g, 8.72 mmol) in pyridine (20 mL), under nitrogen atmosphere. After stirring overnight at room temperature, ethyl acetate was added and the solution was washed with 10% HCl (2 times). The phases were separated and the organics were dried over sodium sulphate and evaporated to dryness under reduced pressure.

The title compound was used for the next step without further purification.
Yield: quantitative; LCMS (RT): 4.48 min (Method A); MS (ES+) gave m/z: 211.1.

1 (C) (S)-3-(N-Hydroxycarbamimidoyl)-piperidine-1-carboxylic acid tert-butyl ester

A solution of (S)-3-cyano-piperidine-1-carboxylic acid tert-butyl ester (1.8 g, 8.72 mmol) and aqueous hydroxylamine (50% in water, 2.1 mL, 34.88 mmol) in ethanol (20 mL) was refluxed for 2h. The solvent was evaporated under reduced pressure to afford the title compound that was used for the next step without further purification.
Yield: quantitative; LCMS (RT): 2.71 min (Method A); MS (ES+) gave m/z: 244.0.

1 (D) (S)-3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine-1-carboxylic acid tert-butyl ester

A mixture of (S)-3-(N-hydroxycarbamimidoyl)-piperidine-1-carboxylic acid tert-butyl ester (500 mg, 2.05 mmol), 4-fluorobenzoic acid (0.288 g, 2.05 mmol), HOBT (0.277 g, 2.05 mmol), EDCI.HCl (0.590 g, 3.08 mmol) and dry triethylamine (0.571 mL, 4.1 mmol) in dry dioxane (5 mL) was kept under stirring at ambient temperature for 20h, under nitrogen atmosphere. The reaction mixture was then refluxed for 2h and the solvent was evaporated under reduced pressure. The residue was diluted with water (40 mL) and ethyl acetate (40 mL), the phases were separated and the organic layer was washed sequentially with water (40 mL, twice), $Na_2CO_3$ 1N (40 mL, twice) and with brine. The organic layer was dried over sodium sulphate and the solvent was removed under vacuum to give a residue that was purified by flash chromatography (silica gel, eluent: petroleum ether/ethyl acetate 9:1) to give the pure title compound (161 mg).
Yield: 23%; LCMS (RT): 6.65 min (Method A); MS (ES+) gave m/z: 348.0.

1 (E) (S)-3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride

To a solution of (S)-3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine-1-carboxylic acid tert-butyl ester (0.160 g, 0.46 mmol) in dichloromethane (5 mL), 1.5 mL of 4N HCl (dioxane solution) were added at 0°C and the reaction mixture was allowed to warm at room temperature and stirred for 1.5h. The solvent was evaporated under reduced pressure to give the title compound as a white solid, which was used for the next step without further purification.
Yield: quantitative; LCMS (RT): 3.03 min (Method A); MS (ES+) gave m/z: 248.0.

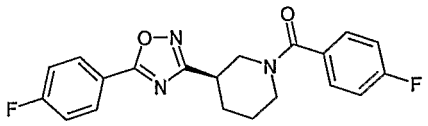
1 (F) (4-Fluoro-phenyl)-{(S)-3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone

To a suspension of (S)-3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (114 mg, 0.46 mmol) in dry dichloromethane (10 mL), triethylamine (128 uL, 0.92 mmol) and 4-fluorobenzoyl chloride (65 µL, 0.55 mmol) were added dropwise at 0°C. The reaction mixture was allowed to warm at room temperature and stirred for 2h under nitrogen atmosphere. The solution was then treated with water (5 mL) and the phases were separated. The organic layer was washed subsequently with 1N HCl (10 mL, 2 times), 5% $NaHCO_3$ (10 mL, twice), then was dried over $Na_2SO_4$ and evaporated under reduced pressure. The crude was purified by flash chromatography (silica gel, eluent: petroleum ether/ethyl acetate 7:3) to give the pure title compound (79 mg) as a white solid.

Yield: 47%; mp=157-160°C; $[\alpha]_D^{20}$ = +65.4° (c=0.4, MeOH); LCMS (RT): 7.54 min (Method E); MS (ES+) gave m/z: 370.1
H-NMR (DMSO-$d_6$, 300 MHz), δ (ppm): 8.13 (dd, 2H); 7.50-7.39 (m, 4H); 7.22 (dd, 2H); 4.23 (m, 1H); 3.81 (m, 1H); 3.40 (dd, 1H); 3.25 (ddd, 1H); 3.14 (m, 1H); 2.21 (m, 1H); 1.99-1.76 (m, 2H); 1.65 (m, 1H).

Example 2

(4-Fluoro-phenyl)-{(R)-3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone



2 (A) (R)-3-Carbamoyl-piperidine-1-carboxylic acid tert-butyl ester

Triethylamine (304 µL, 2.18 mmol) and then ethyl chloroformate (0.22 mL, 2.29 mmol) were added dropwise at 0°C to a solution of (R)-1-Boc-piperidine-3-carboxylic acid (0.5 g, 2.18 mmol) in chloroform (10 mL), under nitrogen atmosphere. After stirring 10 min at 0°C, $NH_3$ (gas) was bubbled into the solution for 1h. The reaction mixture was then stirred at room temperature for 3h, 5% $NaHCO_3$ (aq) was added and the phases were separated. The organic layer was dried over sodium sulphate and evaporated under reduced pressure to afford the title compound, which was used for the next step without further purification.
Yield: quantitative; LCMS (RT): 3.31. min (Method A); MS (ES+) gave m/z: 229.0.

2 (B) (R)-3-Cyano-piperidine-1-carboxylic acid tert-butyl ester

Phosphorus oxychloride (203 µL, 2.18 mmol) was added dropwise at 0°C to a solution of (R)-3-carbamoyl-piperidine-1-carboxylic acid tert-butyl ester (0.5 g, 2.18 mmol) in pyridine (10 mL), under nitrogen atmosphere. After stirring overnight at room temperature, ethyl acetate was added and the solution was washed with 10% HCl (2 times). The phases were separated and the organics were dried over sodium sulphate and evaporated to dryness under reduced pressure.
The title compound was used for the next step without further purification.
Yield: quantitative; LCMS (RT): 4.48 min (Method A); MS (ES+) gave m/z: 211.1.

2 (C) (R)-3-(N-Hydroxycarbamimidoyl)-piperidine-1-carboxylic acid tert-butyl ester

A solution of (R)-3-cyano-piperidine-1-carboxylic acid tert-butyl ester (457 g, 2.18 mmol) and aqueous hydroxylamine (50% in water, 0.534 mL, 8.72 mmol) in ethanol (10 mL) was refluxed for 2h. The solvent was evaporated under reduced pressure to afford the title compound that was used for the next step without further purification.
Yield: 80%; LCMS (RT): 2.71 min (Method A); MS (ES+) gave m/z: 244.0.

2 (D) (R)-3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine-1-carboxylic acid tert-butyl ester

A mixture of (R)-3-(N-hydroxycarbamimidoyl)-piperidine-1-carboxylic acid tert-butyl ester (423 mg, 1.74 mmol), 4-fluorobenzoic acid (0.244 g, 1.74 mmol), HOBT (235 mg, 1.74 mmol), EDCI.HCl (500 mg, 2.61 mmol) and dry triethylamine (0.485 mL, 3.48 mmol) in dry dioxane (5 mL) was kept under stirring at ambient

temperature for 20h, under nitrogen atmosphere. The reaction mixture was then refluxed for 2h and the solvent was evaporated under reduced pressure. The residue was diluted with water (40 mL) and ethyl acetate (40 mL), the phases were separated and the organic layer was washed sequentially with water (40 mL, twice), 1N $Na_2CO_3$ (40 mL, twice) and with brine. The organic layer was dried over sodium sulphate and the solvent was removed under vacuum to give a residue that was purified by flash chromatography (silica gel, eluent: petroleum ether/ethyl acetate 9:1) to give the pure title compound (263 mg).
Yield: 44%; LCMS (RT): 6.65 min (Method A); MS (ES+) gave m/z: 348.0.

2 (E) (R)-3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride

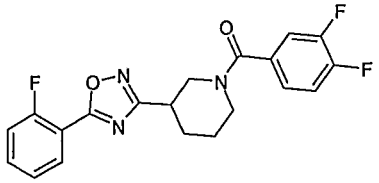
To a solution of (R)-3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine-1-carboxylic acid tert-butyl ester (100 mg, 0.29 mmol) in dichloromethane (5 mL), 1 mL of 4N HCl (dioxane solution) was added at 0°C and the reaction mixture was allowed to warm at room temperature and stirred for 1.5h. The solvent was evaporated under reduced pressure to give the title compound as a white solid, which was used for the next step without further purification.
Yield: quantitative; LCMS (RT): 3.03 min (Method A); MS (ES+) gave m/z: 248.0.

2 (F) (4-Fluoro-phenyl)-{(R)-3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone

To a suspension of (R)-3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (71 mg, 0.29 mmol) in dry dichloromethane (5 mL), triethylamine (0.121 mL, 0.87 mmol) and 4-fluorobenzoyl chloride (41 µL, 0.35 mmol) were added dropwise at 0°C. The reaction mixture was allowed to warm at room temperature and stirred for 2h under nitrogen atmosphere. The solution was then treated with water (5 mL) and the phases were separated. The organic layer was washed subsequently with 1N HCl (10 mL, 2 times), 5% $NaHCO_3$ (10 mL, twice), then was dried over $Na_2SO_4$ and evaporated under reduced pressure. The crude was purified by flash chromatography (silica gel, eluent: petroleum ether/ethyl acetate 7:3) to give the pure title compound (79 mg) as a white solid.
Yield: 51%; mp= 120-123°C; $[\alpha]_D^{20}$ = - 76.38° (c=0.7, MeOH); LCMS (RT): 7.17 min (Method E); MS (ES+) gave m/z: 370.1
$^1$H-NMR (DMSO-$d_6$,), δ (ppm): 8.13 (dd, 2H); 7.50-7.39 (m, 4H); 7.22 (dd, 2H); 4.24 (m, 1H); 3.81 (m, 1H); 3.40 (dd, 1H); 3.29-3.09 (m, 2H); 2.21 (m, 1H); 1.99-1.76 (m, 2H); 1.64 (m, 1H).

Example 3

(3,4-Difluoro-phenyl)-{3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone




3 (A) 3-Carbamoyl-piperidine-1-carboxylic acid tert-butyl ester

Triethylamine (0.96 mL, 6.89 mmol) and then ethyl chloroformate (0.69 mL, 7.23 mmol) were added dropwise at 0°C to a solution of 1-Boc-piperidine-3-

carboxylic acid (1.58 g, 6.89 mmol) in chloroform (10 mL), under nitrogen atmosphere. After stirring 10 min at 0°C, $NH_3$ (gas) was bubbled into the solution for 1h. The reaction mixture was then stirred at room temperature for 3h, 5% $NaHCO_3$ (aq) was added and the phases were separated. The organic layer was dried over sodium sulphate and evaporated under reduced pressure to afford the title compound, which was used for the next step without further purification.
Yield: quantitative; LCMS (RT): 3.31 min (Method A); MS (ES+) gave m/z: 229.0.

3 (B) 3-Cyano-piperidine-1-carboxylic acid tert-butyl ester

Phosphorus oxychloride (0.64 mL, 6.89 mmol) was added dropwise at 0°C to a solution of 3-carbamoyl-piperidine-1-carboxylic acid tert-butyl ester (1.58 g, 6.89 mmol) in pyridine (15 mL), under nitrogen atmosphere. After stirring overnight at room temperature, ethyl acetate was added and the solution was washed with 10% HCl (2 times). The phases were separated and the organics were dried over sodium sulphate and evaporated to dryness under reduced pressure.
The title compound was used for the next step without further purification.
Yield: quantitative; LCMS (RT): 4.48 min (Method A); MS (ES+) gave m/z: 211.1.

3 (C) 3-(N-Hydroxycarbamimidoyl)-piperidine-1-carboxylic acid tert-butyl ester

A solution of 3-cyano-piperidine-1-carboxylic acid tert-butyl ester (1.4 g, 6.89 mmol) and aqueous hydroxylamine (50% in water, 1.7 mL, 27.5 mmol) in ethanol (15 mL) was refluxed for 2h. The solvent was evaporated under reduced pressure to afford the title compound that was used for the next step without further purification.
Yield: quantitative; LCMS (RT): 2.71 min (Method A); MS (ES+) gave m/z: 244.0.

3 (D) 3-[5-(2-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine-1-carboxylic acid tert-butyl ester

A mixture of 3-(N-hydroxycarbamimidoyl)-piperidine-1-carboxylic acid tert-butyl ester (1 g, 4.1 mmol), 2-fluorobenzoic acid (574 mg, 4.1 mmol), HOBT (554 mg, 4.1 mmol), EDCI.HCl (1.18 g, 6.15 mmol) and dry triethylamine (1.14 mL, 8.2 mmol) in dry dioxane (15 mL) was kept under stirring at ambient temperature for 20h, under nitrogen atmosphere. The reaction mixture was then refluxed for 2h and the solvent was evaporated under reduced pressure. The residue was diluted with water (40 mL) and ethyl acetate (40 mL), the phases were separated and the organic layer was washed sequentially with water (40 mL, twice), 1N $Na_2CO_3$ (40 mL, twice) and with brine. The organic layer was dried over sodium sulphate and the solvent was removed under vacuum to give a residue that was purified by flash chromatography (silica gel, eluent: petroleum ether/ethyl acetate 9:1) to give the pure title compound (524 mg).
Yield: 35%; LCMS (RT): 6.48 min (Method A); MS (ES+) gave m/z: 370.0.

3 (E) 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride

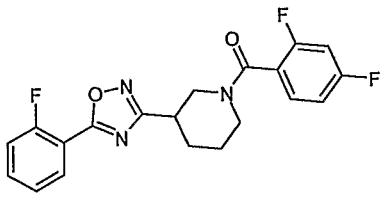
To a solution of 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine-1-carboxylic acid tert-butyl ester (0.524 g, 1.5 mmol) in dichloromethane (5 mL), 1.5 mL of 4N HCl (dioxane solution) were added at 0°C and the reaction mixture was allowed to warm at room temperature and stirred for 1.5h. The solvent was evaporated under reduced pressure to give the title compound as a white solid, which was used for the next step without further purification.
Yield: quantitative; LCMS (RT): 2.84 min (Method A); MS (ES+) gave m/z: 248.0.

3 (F) (3,4-Difluoro-phenyl)-{3-[5-(2-fluoro-phenyl)-1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone

To a suspension of 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (51 mg, 0.21 mmol) in dry dichloromethane (5 mL), triethylamine (88 µL, 0.63 mmol) and 3,4-difluorobenzoyl chloride (65 µL, 0.55 mmol) were added dropwise at 0°C. The reaction mixture was allowed to warm at room temperature and stirred for 2h under nitrogen atmosphere. The solution was then treated with water (5 mL) and the phases were separated. The organic layer was washed subsequently with 1N HCl (10 mL, 2 times), 5% $NaHCO_3$ (10 mL, twice), then was dried over $Na_2SO_4$ and evaporated under reduced pressure. The crude was purified by flash chromatography (silica gel, eluent: petroleum ether/ethyl acetate 7:3) to give the pure title compound (79 mg) as a white solid.
Yield: 47%; mp= 80-83°C; LCMS (RT): 7.64 min (Method E); MS (ES+) gave m/z: 388.1.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.07 (dd, 1H); 7.75 (m, 1H); 7.52-7.38 (m, 4H); 7.27 (m, 1H); 4.21 (m, 1H); 3.78 (m, 1H); 3.43 (dd, 1H); 3.33-3.17 (m, 2H); 2.21 (m, 1H); 2.00-1.76 (m, 2H); 1.65 (m, 1H).

Example 4

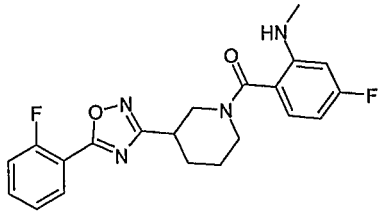
(2,4-Difluoro-phenyl)-{3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone



The compound was prepared following the procedure described in the Example 3 (F), using 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (prepared as described in the Example 3 (E)) and 2,4-difluorobenzoyl chloride. Purification of the final compound was performed by flash chromatography on silica gel (eluent: AcOEt, hexane 5:5)
Yield: quantitative (white gummy solid); LCMS (RT): 7.62 min (Method E); MS (ES+) gave m/z: 388.1.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.08 (m, 1H); 7.75 (m, 1H); 7.52-7.41 (m, 3H); 7.22 (dd, 1H); 7.12 (dd, 1H); 4.53 (m br, 1H); 3.89 (m br, 1H); 3.42 (m, 1H); 3.27 (m, 1H); 3.17 (m, 1H); 2.22 (m, 1H); 2.02-1.77 (m, 2H); 1.62 (m, 1H).

Example 5

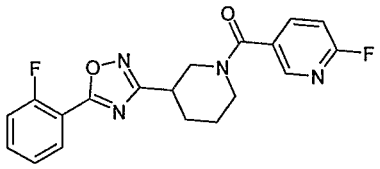
(4-Fluoro-2-methylamino-phenyl)-{3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone



A mixture of 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (51 mg, 0.21 mmol, prepared as described in the Example 3 (E)), 4-fluoro-2-methylamino-benzoic acid (43 mg, 0.25 mmol), EDCI.HCl (60 mg, 0.32 mmol), HOBT (28 mg, 0.21 mmol) and TEA (0.088 mL, 0.63 mmol) in dioxane (10 mL) was stirred overnight at room temperature, under nitrogen atmosphere. The solvent was evaporated under reduced pressure. The residue was diluted with water (5 mL) and ethyl acetate (10 mL), the phases were separated and the organic layer was washed with 2N $Na_2CO_3$ (5 mL x 2 times) and dried over $Na_2SO_4$. Evaporation of the solvent under reduced pressure gave a crude solid that was purified by flash chromatography (silica gel, eluent gradient: from petroleum ether/ethyl acetate 7:3 to petroleum ether/ethyl acetate 1:1).
(4-Fluoro-2-methylamino-phenyl)-{3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone was obtained as a colorless oil (64 mg).
Yield: 75% (colorless oil); LCMS (RT): 7.95 min (Method E); MS (ES+) gave m/z: 399.2
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.07 (ddd, 1H); 7.75 (m, 1H); 7.52-7.41 (m, 2H); 7.06 (dd, 1H); 6.37 (s, 1H); 6.33 (m, 1H); 4.23 (dd, 1H); 3.77 (ddd, 1H); 3.40 (dd, 1H); 3.21 (m, 2H); 2.71 (s, 3H); 2.19 (m, 1H); 1.97-1.75 (m, 2H); 1.62 (m, 1H).

Example 6

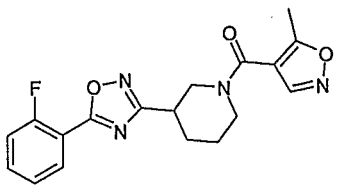
{3-[5-(2-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(5-fluoro-pyridin-2-yl)-methanone



The compound was prepared following the procedure described in the Example 5, using 6-fluoronicotinic acid as the acid of choice and starting from 3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (prepared as described in the Example 3 (E)). Purification of the final compound was performed by flash chromatography on silica gel (eluent gradient: from petroleum ether/ethyl acetate 7:3 to petroleum ether/ethyl acetate 1:1).
Yield: quantitative (white gummy solid); LCMS (RT): 7.07 min (Method E); MS (ES+) gave m/z: 371.2.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.31 (m, 1H); 8.11-7.99 (m, 2H); 7.75 (m, 1H); 7.51-7.41 (m, 2H); 7.21 (dd, 1H); 4.23 (m, 1H); 3.80 (m, 1H); 3.46 (dd, 1H); 3.31 (ddd, 1H); 3.24 (ddd, 1H); 2.22 (m, 1H); 1.94 (m, 1H); 1.82 (m, 1H); 1.68 (m, 1H).

Example 7

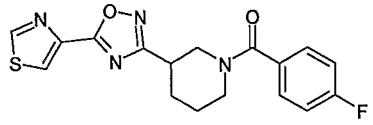
{3-[5-(2-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(5-methyl-isoxazol-4-yl)-methanone



The compound was prepared following the procedure described in the Example 5 using 5-methyl-isoxazole-4-carboxylic acid as the acid of choice and starting from 3-[5-(2-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (prepared as described in the Example 3 (E)). Purification of the final compound was performed by flash chromatography on silica gel (eluent gradient: from petroleum ether/ethyl acetate 7:3 to petroleum ether/ethyl acetate 1:1).
Yield: 95% (white gummy solid); LCMS (RT): 6.90 min (Method E); MS (ES+) gave m/z: 357.1.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.58 (s, 1H); 8.08 (ddd, 1H); 7.76 (m, 1H); 7.53-7.41 (m, 2H); 4.25 (m, 1H); 3.83 (m, 1H); 3.45 (dd, 1H); 3.31 (ddd, 1H); 3.20 (ddd, 1H); 2.47 (s, 3H); 2.22 (m, 1H); 2.01-1.78 (m, 2H); 1.65 (m, 1H).

Example 8

(4-Fluoro-phenyl)-[3-(5-thiazol-4-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone



8 (A) 3-(5-Thiazol-4-yl-[1,2,4]oxadiazol-3-yl)-piperidine-1-carboxylic acid tert-butyl ester

The compound was prepared following the procedure described in the Example 3 (D) using 3-(N-hydroxycarbamimidoyl)-piperidine-1-carboxylic acid tert-butyl ester (prepared as described in Example 3 (C)) and thiazole-4-carboxylic acid. Purification of the final compound was performed by flash chromatography on silica gel (eluent AcOEt:Hexane 1:1).
Yield: 63% (colourless oil); LCMS (RT): 5.1 min (Method A); MS (ES+) gave m/z: 337.0.

8 (B) 3-(5-Thiazol-4-yl-[1,2,4]oxadiazol-3-yl)-piperidine hydrochloride

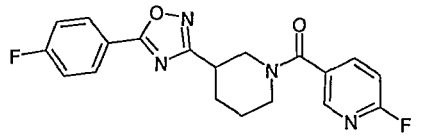
The compound was prepared following the procedure described in the Example 3 (E) starting from 3-(5-thiazol-4-yl-[1,2,4]oxadiazol-3-yl)-piperidine-1-carboxylic acid tert-butyl ester (prepared as described in Example 8 (A))
Yield: quantitative (white powder); LCMS (RT): 1.24 min (Method A); MS (ES+) gave m/z: 237.0.

8 (C) (4-Fluoro-phenyl)-[3-(5-thiazol-4-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone

The compound was prepared following the procedure described in the Example 3 (F), using 3-(5-thiazol-4-yl-[1,2,4]oxadiazol-3-yl)-piperidinehydrochloride (prepared as described in the Example 8 (B)) and 4-fluorobenzoyl chloride. Purification of the final compound was performed by flash chromatography on silica gel (eluent: AcOEt, hexane 4:1)
Yield: 63% (white solid); mp= 128°C; LCMS (RT): 6.18 min (Method E); MS (ES+) gave m/z: 359.1.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 9.32 (d, 1H); 8.71 (d, 1H); 7.48 (dd, 2H); 7.23 (dd, 2H); 4.24 (m, 1H); 3.82 (m, 1H); 3.39 (dd, 1H); 3.29-3.11 (m, 2H); 2.22 (m, 1H); 1.99-1.77 (m, 2H); 1.64 (m, 1H).

Example 9

{3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(6-fluoro-pyridin-3-yl)-methanone



9 (A) 3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine-1-carboxylic acid tert-butyl ester

The compound was prepared following the procedure described in the Example 3 (D) using 3-(N-hydroxycarbamimidoyl)-piperidine-1-carboxylic acid tert-butyl ester (prepared as described in Example 3 (C)) and 4-fluorobenzoic acid. Purification of the final compound was performed by flash chromatography on silica gel (eluent DCM/MeOH 99:1).
Yield: 51% (yellow oil); LCMS (RT): 4.8 min (Method D); MS (ES+) gave m/z: 348.1.

9 (B) 3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride

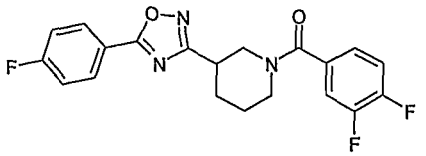
The compound was prepared following the procedure described in the Example 3 (E) starting from 3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine-1-carboxylic acid tert-butyl ester (prepared as described in Example 9 (A))
Yield: 79% (white powder); LCMS (RT): 4.6 min (Method C); MS (ES+) gave m/z: 248.1.

9 (C) {3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(6-fluoro-pyridin-3-yl)-methanone

The compound was prepared following the procedure described in the Example 5 using 6-fluoro-nicotinic acid as the acid of choice and 3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (prepared as described in the Example 9 (B)). Purification of the final compound was performed by trituration with diisopropylether.
Yield: 71% (white solid); mp= 131-134°C; LCMS (RT): 6.77 min (Method E); MS (ES+) gave m/z: 371.1.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.31 (m, 1H); 8.13 (dd, 2H); 8.03 (ddd, 1H); 7.44 (dd, 2H); 7.20 (dd, 1H); 4.23 (m, 1H); 3.80 (m, 1H); 3.44 (dd, 1H); 3.31 (ddd, 1H); 3.21 (ddd, 1H); 2.21 (m, 1H); 1.93 (m, 1H); 1.83 (m, 1H); 1.67 (m, 1H).

Example 10

(3,4-Difluoro-phenyl)-{3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone

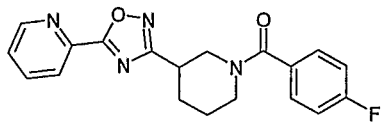


The compound was prepared following the procedure described in the Example 3 (F), using 3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (prepared as described in the Example 9 (B)) and 3,4-difluorobenzoyl chloride. Purification of the final compound was performed by trituration with diisopropylether.

Yield: 81% (white solid); mp= 149-152°C; LCMS (RT): 7.42 min (Method E); MS (ES+) gave m/z: 388.1.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.14 (dd, 2H); 7.50-7.39 (m, 4H); 7.27 (m, 1H); 4.21 (m, 1H); 3.79 (m, 1H); 3.41 (dd, 1H); 3.27 (ddd, 1H); 3.18 (ddd, 1H); 2.21 (m, 1H); 1.92 (m, 1H); 1.82 (m, 1H); 1.65 (m, 1H).

Example 11

(4-Fluoro-phenyl)-[3-(5-pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone



11 (A) 3-(5-Pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidine-1-carboxylic acid tert-butyl ester

The compound was prepared following the procedure described in the Example 3 (D) using 3-(N-hydroxycarbamimidoyl)-piperidine-1-carboxylic acid tert-butyl ester (prepared as described in Example 3 (C)) and pyridine-2-carboxylic acid. Purification of the final compound was performed by flash chromatography on silica gel (eluent AcOEt:hexane 4:6).
Yield: 51% (white solid); LCMS (RT): 4.79 min (Method A); MS (ES+) gave m/z: 331.0.

11 (B) 2-(3-Piperidin-3-yl-[1,2,4]oxadiazol-5-yl)-pyridine dihydrochloride

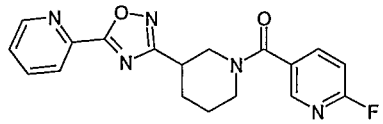
The compound was prepared following the procedure described in the Example 3 (E) starting from 3-(5-pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidine-1-carboxylic acid tert-butyl ester (prepared as described in Example 11 (A)).
Yield: quantitative (white powder); LCMS (RT): 0.71 min (Method A); MS (ES+) gave m/z: 231.1.

11 (C) (4-Fluoro-phenyl)-[3-(5-pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone

The compound was prepared following the procedure described in the Example 3 (F), using 2-(3-piperidin-3-yl-[1,2,4]oxadiazol-5-yl)-pyridine dihydrochloride (prepared as described in the Example 11 (B)) and 4-fluorobenzoyl chloride. Purification of the final compound was performed by flash chromatography on silica gel (eluent: hexane: ACOEt 3:7).
Yield: 64% (white solid); mp= 126-129°C; LCMS (RT): 6.23 min (Method E); MS (ES+) gave m/z: 353.1.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.81 (m, 1H); 8.17 (m, 1H); 8.07 (ddd, 1H); 7.68 (ddd, 1H); 7.47 (dd, 2H); 7.23 (dd, 2H); 4.25 (m, 1H); 3.83 (m, 1H); 3.42 (dd, 1H); 3.30-3.14 (m, 2H); 2.23 (m, 1H); 2.00-1.78 (m, 2H); 1.65 (m, 1H).

Example 12

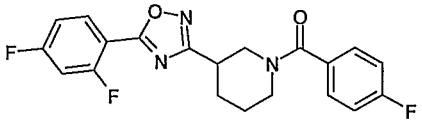
(6-Fluoro-pyridin-3-yl)-[3-(5-pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone



The compound was prepared following the procedure described in the Example 5, using 6-fluoro-nicotinic acid as acid of choice and 2-(3-piperidin-3-yl-[1,2,4]oxadiazol-5-yl)-pyridine dihydrochloride (prepared as described in the Example 11 (B)). Purification of the final compound was performed by flash chromatography on silica gel (eluent: hexane: ACOEt 3:7).
Yield: 50% (white solid); mp= 124-126°C; LCMS (RT): 5.78 min (Method E); MS (ES+) gave m/z: 354.1.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.81 (m, 1H); 8.32 (m, 1H); 8.18 (d, 1H); 8.05 (m, 2H); 7.68 (ddd, 1H); 7.21 (ddd, 1H); 4.24 (m, 1H); 3.81 (m, 1H); 3.47 (dd, 1H); 3.37-3.20 (m, 2H); 2.23 (m, 1H); 1.95 (m, 1H), 1.84 (m, 1H); 1.68 (m, 1H).

Example 13

{3-[5-(2,4-Difluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(4-fluoro-phenyl)-methanone



13 (A) 3-[5-(2,4-Difluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine-1-carboxylic acid tert-butyl ester

The compound was prepared following the procedure described in the Example 3 (D) using 3-(N-hydroxycarbamimidoyl)-piperidine-1-carboxylic acid tert-butyl ester (prepared as described in Example 3 (C)) and 2,4-difluoro-benzoic acid. Purification of the final compound was performed by flash chromatography on silica gel (eluent AcOEt: hexane 1:4).
Yield: 55% (colourless oil); LCMS (RT): 6.61 min (Method A); MS (ES+) gave m/z: 366.0.

13 (B) 3-[5-(2,4-Difluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride

The compound was prepared following the procedure described in the Example 3 (E) starting from 3-[5-(2,4-difluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine-1-carboxylic acid tert-butyl ester (prepared as described in Example 13 (A))
Yield: quantitative (white powder); LCMS (RT): 2.8 min (Method A); MS (ES+) gave m/z: 266.0.

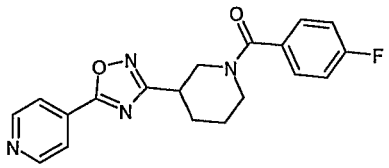
13 (C) {3-[5-(2,4-Difluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(4-fluoro-phenyl)-methanone

The compound was prepared following the procedure described in the Example 3 (F) starting from 3-[5-(2,4-difluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (prepared as described in the Example 13 (B)) and 4-

fluorobenzoyl chloride. Purification of the final compound was performed by flash chromatography on silica gel (eluent AcOEt: hexane 1:3).
Yield: 71% (white solid); mp = 88°C; LCMS (RT): 7.21 min (Method E); MS (ES+) gave m/z: 388.1.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.15 (ddd, 1H); 7.54-7.42 (m, 3H); 7.33 (ddd, 1H); 7.22 (dd, 2H); 4.23 (m, 1H); 3.82 (m, 1H); 3.40 (dd, 1H); 3.30-3.12 (m, 2H); 2.21 (m, 1H); 1.98-1.77 (m, 2H); 1.64 (m, 1H).

Example 14

(4-Fluoro-phenyl)-[3-(5-pyridin-4-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone



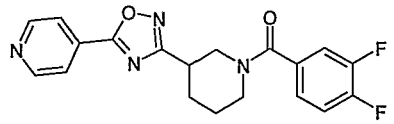
14 (A) 3-(5-Pyridin-4-yl-[1,2,4]oxadiazol-3-yl)-piperidine-1-carboxylic acid tert-butyl ester
The compound was prepared following the procedure described in the Example 3 (D) using 3-(N-hydroxycarbamimidoyl)-piperidine-1-carboxylic acid tert-butyl ester (prepared as described in Example 3 (C)) and pyridine-4-carboxylic acid. Purification of the final compound was performed by flash chromatography on silica gel (eluent AcOEt:hexane 4:6).
Yield: 44% (white solid); LCMS (RT): 5.27 min (Method A); MS (ES+) gave m/z: 331.1.

14 (B) 4-(3-Piperidin-3-yl-[1,2,4]oxadiazol-5-yl)-pyridine dihydrochloride
The compound was prepared following the procedure described in the Example 3 (E) starting from 3-(5-pyridin-4-yl-[1,2,4]oxadiazol-3-yl)-piperidine-1-carboxylic acid tert-butyl ester (prepared as described in Example 14 (A)).
Yield: quantitative (white powder); LCMS (RT): 0.81 min (Method A); MS (ES+) gave m/z: 231.1.

14 (C) (4-Fluoro-phenyl)-[3-(5-pyridin-4-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
The compound was prepared following the procedure described in the Example 3 (F), using 4-(3-piperidin-3-yl-[1,2,4]oxadiazol-5-yl)-pyridine dihydrochloride (prepared as described in the Example 14 (B)) and 4-fluorobenzoyl chloride. Purification of the final compound was performed by flash chromatography on silica gel (eluent: hexane: ACOEt 3:7).
Yield: 65% (white solid); mp=149-151°C; LCMS (RT): 5.79 min (Method E); MS (ES+) gave m/z: 353.1.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.87 (d, 2H); 7.97 (d, 2H); 7.46 (dd, 2H); 7.22 (dd, 2H); 4.25 (m, 1H); 3.81 (m, 1H); 3.43 (dd, 1H); 3.31-3.14 (m, 2H); 2.22 (m, 1H); 2.00-1.78 (m, 2H); 1.65 (m, 1H).

Example 15

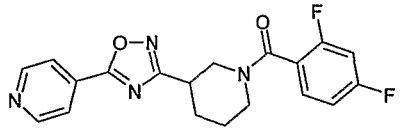
(3,4-Difluoro-phenyl)-[3-(5-pyridin-4-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone



The compound was prepared following the procedure described in the Example 3 (F), using 4-(3-piperidin-3-yl-[1,2,4]oxadiazol-5-yl)-pyridine dihydrochloride (prepared as described in the Example 14 (B)) and 3,4-difluorobenzoyl chloride. Purification of the final compound was performed by flash chromatography on silica gel (eluent: hexane: AcOEt 3:7).
Yield: 45% (white solid); mp = 132-134°C; LCMS (RT): 5.96 min (Method E); MS (ES+) gave m/z: 371.1.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.87 (d, 2H); 7.96 (d, 2H); 7.45 (m, 2H); 7.27 (m, 1H); 4.22 (m, 1H); 3.78 (m, 1H); 3.43 (dd, 1H); 3.33-3.17 (m, 2H); 2.22 (m, 1H); 2.00-1.76 (m, 2H); 1.66 (m, 1H).

Example 16

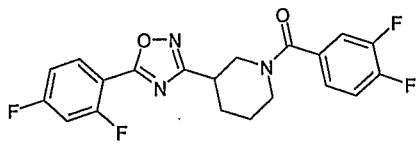
(2,4-Difluoro-phenyl)-[3-(5-pyridin-4-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone



The compound was prepared following the procedure described in the Example 3 (F), using 4-(3-piperidin-3-yl-[1,2,4]oxadiazol-5-yl)-pyridine hydrochloride (prepared as described in the Example 14 (B)) and 2,4-difluorobenzoyl chloride. Purification of the final compound was performed by flash chromatography on silica gel (eluent: hexane: ACOEt 3:7)
Yield: 71% (white solid); mp=137-139°C; LCMS (RT): 5.89 min (Method E); MS (ES+) gave m/z: 371.1.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.86 (d, 2H); 7.95 (d br, 2H); 7.46 (ddd, 1H); 7.23 (ddd, 1H); 7.13 (ddd, 1H); 4.52 (m br, 1H); 4.01 (m br, 1H); 3.43 (m, 1H); 3.27 (m, 1H); 3.18 (m, 1H); 2.22 (m, 1H); 2.02-1.77 (m, 2H); 1.62 (m, 1H).

Example 17

(3,4-Difluoro-phenyl)-{3-[5-(2,4-difluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone

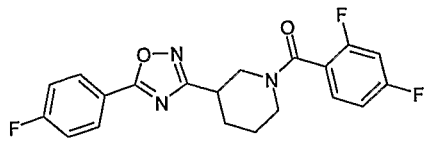


The compound was prepared following the procedure described in the Example 3 (F) starting from 3-[5-(2,4-difluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (prepared as described in the Example 13 (B)) and 3,4-difluorobenzoyl chloride. Purification of the final compound was performed by flash chromatography on silica gel (eluent AcOEt: hexane 1:3).

Yield: 70% (white solid); mp= 91°C; LCMS (RT): 7.37 min (Method E); MS (ES+) gave m/z: 406.1.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.15 (ddd, 1H); 7.54-7.40 (m, 3H); 7.37-7.24 (m, 2H); 4.21 (m, 1H); 3.79 (m, 1H); 3.42 (dd, 1H); 3.33-3.14 (m, 2H); 2.21 (m, 1H); 1.99-1.76 (m, 2H); 1.66 (m, 1H).

Example 18

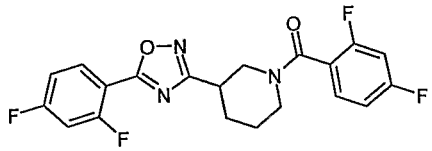
(2,4-Difluoro-phenyl)-{3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone



The compound was prepared following the procedure described in the Example 3 (F), using 3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (prepared as described in the Example 9 (B)) and 2,4-difluorobenzoyl chloride. Purification of the final compound was performed by trituration with diisopropylether.
Yield: 81% (white solid); mp= 137-139°C; LCMS (RT): 7.37 min (Method E); MS (ES+) gave m/z: 388.1.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.13 (m, 2H); 7.44 (dd, 2H); 7.43 (m, 1H); 7.23 (ddd, 1H); 7.12 (ddd, 1H); 4.50 (m br, 1H); 3.96 (m br, 1H); 3.41 (m, 1H); 3.26 (m, 1H); 3.12 (m, 1H); 2.21 (m, 1H); 2.01-1.77 (m, 2H); 1.63 (m, 1H).

Example 19

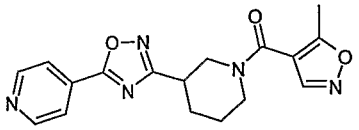
(2,4-Difluoro-phenyl)-{3-[5-(2,4-difluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone



The compound was prepared following the procedure described in the Example 3 (F) starting from 3-[5-(2,4-difluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (prepared as described in the Example 13 (B)) and 2,4-difluorobenzoyl chloride. Purification of the final compound was performed by flash chromatography on silica gel (eluent AcOEt: hexane 1:3).
Yield: 74% (white solid); mp=101 °C; LCMS (RT): 7.32 min (Method E); MS (ES+) gave m/z: 406.1.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.15 (m, 1H); 7.45-7.41 (m, 2H); 7.33 (ddd, 1H); 7.23 (ddd, 1H); 7.12 (ddd, 1H); 4.54 (m br, 1H); 3.97 (m br, 1H); 3.41 (m, 1H); 3.26 (m, 1H); 3.15 (m, 1H); 2.21 (m, 1H); 2.01-1.77 (m, 2H); 1.63 (m, 1H).

Example 20

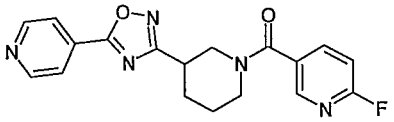
(5-Methyl-isoxazol-4-yl)-[3-(5-pyridin-4-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone



The compound was prepared following the procedure described in the Example 5, using 5-methyl-isoxazole-4-carboxylic acid as acid of choice and starting from 4-(3-piperidin-3-yl-[1,2,4]oxadiazol-5-yl)-pyridine hydrochloride (prepared as described in the Example 14 (B)). Purification of the final compound was performed by flash chromatography on silica gel (eluent: hexane: AcOEt 3:7).
Yield: 55% (off-white solid); LCMS (RT): 5.32 min (Method E); MS (ES+) gave m/z: 340.1.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.88 (d, 2H); 8.58 (s, 1H); 7.97 (d, 2H); 4.26 (m, 1H); 3.83 (m, 1H); 3.46 (dd, 1H); 3.31 (ddd, 1H); 3.22 (ddd, 1H); 2.47 (s, 3H); 2.22 (m, 1H); 1.96 (m, 1H); 1.85 (m, 1H); 1.65 (m, 1H).

Example 21

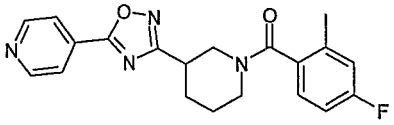
(6-Fluoro-pyridin-3-yl)-[3-(5-pyridin-4-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone



The compound was prepared following the procedure described in the Example 5, using 6-fluoro-nicotinic acid as acid of choice and starting from 4-(3-piperidin-3-yl-[1,2,4]oxadiazol-5-yl)-pyridine dihydrochloride (prepared as described in the Example 14 (B)). Purification of the final compound was performed by flash chromatography on silica gel (eluent: hexane: AcOEt 3:7).
Yield: 47% (white solid); mp=132-134°C; LCMS (RT): 5.38 min (Method E); MS (ES+) gave m/z: 354.1.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.87 (d, 2H); 8.31 (m, 1H); 8.03 (ddd, 1H); 7.96 (d, 2H); 7.21 (dd, 1H); 4.25 (m, 1H); 3.80 (m, 1H); 3.47 (dd, 1H); 3.37-3.21 (m, 2H); 2.22 (m, 1H); 1.95 (m, 1H); 1.82 (m, 1H); 1.68 (m, 1H).

Example 22

(4-Fluoro-2-methyl-phenyl)-[3-(5-pyridin-4-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone

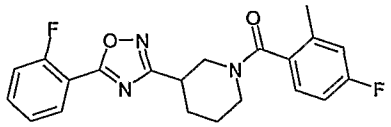


The compound was prepared following the procedure described in the Example 5, using 4-fluoro-2-methyl-benzoic acid as acid of choice and starting from 4-(3-piperidin-3-yl-[1,2,4]oxadiazol-5-yl)-pyridine dihydrochloride (prepared as described in the Example 14 (B)). Purification of the final compound was performed by flash chromatography on silica gel (eluent: hexane: AcOEt 3:7).

Yield: 37% (white gummy solid); LCMS (RT): 5.96 min (Method E); MS (ES+) gave m/z: 367.1.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.87 (d, 2H); 7.96 (d br, 2H); 7.22 (m, 1H); 7.11-6.96 (m, 2H); 4.51 (m br, 1H); 4.02 (m br, 1H); 3.41 (dd, 1H); 3.29-3.10 (m, 2H); 2.23 (s, 3H); 2.19 (m, 1H); 1.92 (m, 1H); 1.79 (m, 1H); 1.60 (m, 1H).

Example 23

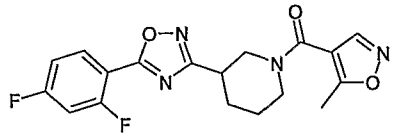
(4-Fluoro-2-methyl-phenyl)-{3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone



The compound was prepared following the procedure described in the Example 5,using 4-fluoro-2-methyl-benzoic acid as the acid of choice and starting from 3-[5-(2-fluorophenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (prepared as described in the Example 3 (E)). Purification of the final compound was performed by flash chromatography on silica gel (eluent gradient: from petroleum ether/ethyl acetate 7:3 to petroleum ether/ethyl acetate 1:1).
Yield: 77% (colourless oil); LCMS (RT): 7.8 min (Method E); MS (ES+) gave m/z: 384.1.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.07 (m, 1H); 7.75 (m, 1H); 7.52-7.39 (m, 2H); 7.22 (m, 1H); 7.12-6.95 (m, 2H); 4.36 (m br, 1H); 3.78 (m br, 1H); 3.40 (dd, 1H); 3.27-3.08 (m, 2H); 2.23 (s, 3H); 2.20 (m, 1H); 1.98-1.74 (m, 2H); 1.60 (m, 1H).

Example 24

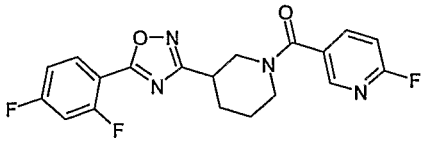
{3-[5-(2,4-Difluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(5-methyl-isoxazol-4-yl)-methanone



The compound was prepared following the procedure described in the Example 5 using 5-methyl-isoxazole-4-carboxylic acid as acid of choice and starting from 3-[5-(2,4-difluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (prepared as described in the Example 13 (B)). Purification of the final compound was performed by flash chromatography on silica gel (eluent AcOEt: hexane 1:1).
Yield: 46% (white solid); mp=79 °C; LCMS (RT): 6.67 min (Method E); MS (ES+) gave m/z: 375.2.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.58 (s, 1H); 8.16 (m, 1H); 7.50 (ddd, 1H); 7.33 (ddd, 1H); 4.25 (m, 1H); 3.83 (m, 1H); 3.44 (dd, 1H); 3.31 (ddd, 1H); 3.19 (ddd, 1H); 2.47 (s, 3H); 2.21 (m, 1H); 2.01-1.76 (m, 2H); 1.65 (m, 1H).

Example 25

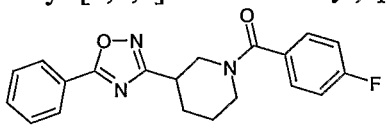
{3-[5-(2,4-Difluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(6-fluoro-pyridin-3-yl)-methanone



The compound was prepared following the procedure described in the Example 5 using 6-fluoro-nicotinic acid as acid of choice and starting from 3-[5-(2,4-difluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (prepared as described in the Example 13 (B)). Purification of the final compound was performed by flash chromatography on silica gel (eluent AcOEt: hexane 1:1).
Yield: 56% (white solid); mp=87 °C; LCMS (RT): 6.74 min (Method E); MS (ES+) gave m/z: 389.1.
$^1$H-NMR (DMSO-$d_6$, 300 MHz), δ (ppm): 8.31 (m, 1H); 8.15 (m, 1H); 8.03 (ddd, 1H); 7.50 (ddd, 1H); 7.33 (m, 1H); 7.21 (ddd, 1H); 4.22 (m, 1H); 3.79 (m, 1H); 3.45 (dd, 1H); 3.31 (ddd, 1H); 3.24 (ddd, 1H); 2.22 (m, 1H); 1.94 (m, 1H); 1.83 (m, 1H); 1.68 (m, 1H).

Example 26

(4-Fluoro-phenyl)-[3-(5-phenyl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone



26 (A) 3-[5-(Phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine-1-carboxylic acid tert-butyl ester

The compound was prepared following the procedure described in the Example 3 (D) using 3-(N-hydroxycarbamidoyl)-piperidine-1-carboxylic acid tert-butyl ester (prepared as described in Example 3 (C)) and benzoic acid. Purification of the final compound was performed by flash chromatography on silica gel (eluent DCM/MeOH 99:1).
Yield: 47% (white solid); LCMS (RT): 4.1 min (Method D); MS (ES+) gave m/z: 330.1.

26 (B) 3-[5-(Phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride

The compound was prepared following the procedure described in the Example 3 (E) starting from 3-[5-(phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine-1-carboxylic acid tert-butyl ester (prepared as described in Example 26 (A)).
Yield: quantitative (white powder); LCMS (RT): 4.4 min (Method C); MS (ES+) gave m/z: 230.1.

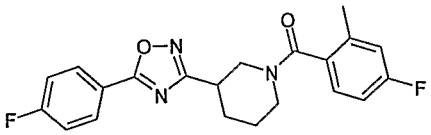
26 (C) (4-Fluoro-phenyl)-[3-(5-phenyl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone

The compound was prepared following the procedure described in the Example 3 (F), using 3-[5-(phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (prepared as described in the Example 26 (B)) and 4-fluorobenzoyl chloride.

Purification of the final compound was performed by flash chromatography on silica gel (eluent: DCM:MeOH 99:1).
Yield: 8% (white solid); LCMS (RT): 7.16 min (Method E); MS (ES+) gave m/z: 352.1.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.07 (d, 2H); 7.74-7.57 (m, 3H); 7.47 (dd, 2H); 7.22 (dd, 2H); 4.24 (m, 1H); 3.82 (m, 1H); 3.41 (dd, 1H); 3.31-3.11 (m, 2H); 2.22 (m, 1H); 1.99-1.76 (m, 2H); 1.64 (m, 1H).

Example 27

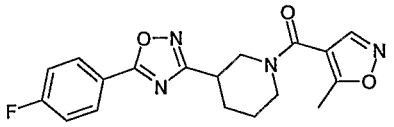
(4-Fluoro-2-methyl-phenyl)-{3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone



The compound was prepared following the procedure described in the Example 5 using 4-fluoro-2-methyl-benzoic acid as the acid of choice and 3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (prepared as described in the Example 9 (B)). Purification of the final compound was performed by flash chromatography on silica gel (eluent: DCM:MeOH 99:1).
Yield: 23% (white solid); mp=129-131°C; LCMS (RT): 7.45 min (Method E); MS (ES+) gave m/z: 384.1.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.13 (m, 2H); 7.44 (dd, 2H); 7.22 (m, 1H); 7.12-6.95 (m, 2H); 4.53 (m br, 1H); 4.07 (m br, 1H); 3.39 (dd, 1H); 3.27-3.05 (m, 2H); 2.23 (s, 3H); 2.20 (m, 1H); 2.01-1.71 (m, 2H); 1.60 (m, 1H).

Example 28

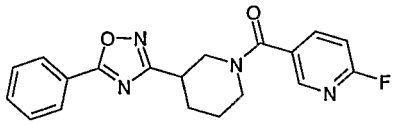
{3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(5-methyl-isoxazol-4-yl)-methanone



The compound was prepared following the procedure described in the Example 5 using 5-methyl-isoxazole-4-carboxylic acid as the acid of choice and 3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (prepared as described in the Example 9 (B)). Purification of the final compound was performed by flash chromatography on silica gel (eluent: DCM:MeOH 99:1).
Yield: 44%; mp=105-107°C; LCMS (RT): 6.7 min (Method E); MS (ES+) gave m/z: 357.1.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.58 (s, 1H); 8.14 (dd, 2H); 7.44 (dd, 2H); 4.25 (m, 1H); 3.83 (m, 1H); 3.44 (dd, 1H); 3.31 (ddd, 1H); 3.17 (ddd, 1H); 2.47 (s, 3H); 2.21 (m, 1H); 2.01-1.77 (m, 2H); 1.64 (m, 1H).

Example 29

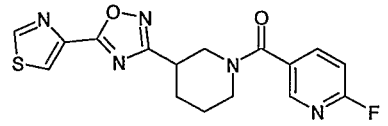
(6-Fluoro-pyridin-3-yl)-[3-(5-phenyl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone



The compound was prepared following the procedure described in the Example 5 using 6-fluoro-nicotinic acid as the acid of choice and 3-[5-(phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (prepared as described in the Example 26 (B)). Purification of the final compound was performed by trituration with diisopropylether.
Yield: 79% (white solid); mp=109-111°C; LCMS (RT): 6.6 min (Method E); MS (ES+) gave m/z: 353.1.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.31 (m, 1H); 8.04 (m, 3H); 7.74-7.58 (m, 3H); 7.21 (dd, 1H); 4.23 (m, 1H); 3.80 (m, 1H); 3.45 (dd, 1H); 3.37-3.15 (m, 2H); 2.22 (m, 1H); 1.94 (m, 1H); 1.83 (m, 1H); 1.67 (m, 1H).

Example 30

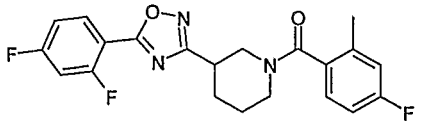
(6-Fluoro-pyridin-3-yl)-[3-(5-thiazol-4-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone



The compound was prepared following the procedure described in the Example 5 using 6-fluoro-nicotinic acid as the acid of choice and 3-(5-thiazol-4-yl-[1,2,4]oxadiazol-3-yl)-piperidine hydrochloride (prepared as described in the Example 8 (B)). Purification of the final compound was performed by flash chromatography on silica gel (eluent AcOEt:hexane 4:1).
Yield: 65% (white solid); mp= 90°C; LCMS (RT): 5.75 min (Method E); MS (ES+) gave m/z: 360.1.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 9.32 (d, 1H); 8.71 (d, 1H); 8.32 (d, 1H); 8.04 (dt, 1H); 7.21 (dd, 1H); 4.24 (m, 1H); 3.81 (m, 1H); 3.45 (dd, 1H); 3.36-3.17 (m, 2H); 2.22 (m, 1H); 1.94 (m, 1H); 1.83 (m, 1H); 1.67 (m, 1H).

Example 31

{3-[5-(2,4-Difluoro-phenyl)-[1,2,4] oxadiazol-3-yl]-piperidin-1-yl}-(4-fluoro-2-methyl-phenyl)-methanone

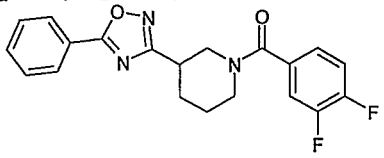


The compound was prepared following the procedure described in the Example 5 using 4-fluoro-2-methyl-benzoic acid as acid of choice and starting from 3-[5-(2,4-difluorophenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (prepared as described in the Example 13 (B)). Purification of the final compound was performed by flash chromatography on silica gel (eluent AcOEt: hexane 1:3).

Yield: 58% (white solid); mp= 110°C; LCMS (RT): 7.29 min (Method E); MS (ES+) gave m/z: 402.2.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.14 (m br, 1H); 7.50 (ddd, 1H); 7.33 (ddd, 1H); 7.22 (m, 1H); 7.04 (m, 2H); 4.54 (m br, 1H); 4.09 (m br, 1H); 3.38 (dd, 1H); 3.28-3.08 (m, 2H); 2.22 (s, 3H); 2.19 (m, 1H); 1.98-1.73 (m, 2H); 1.60 (m, 1H).

Example 32

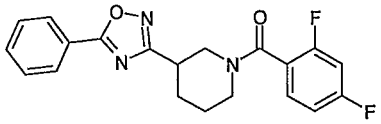
(3,4-Difluoro-phenyl)-[3-(5-phenyl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone



The compound was prepared following the procedure described in the Example 3 (F), using 3-[5-(phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (prepared as described in the Example 26 (B)) and 3,4-difluorobenzoyl chloride. Purification of the final compound was performed by flash chromatography on silica gel (eluent: DCM:MeOH 99:1)
Yield: 78% (white solid); mp=116-118°C; LCMS (RT): 7.27 min (Method E); MS (ES+) gave m/z: 370.1.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.07 (d, 2H); 7.70 (dd, 1H); 7.62 (dd, 2H); 7.51-7.39 (m, 2H); 7.27 (m, 1H); 4.21 (m, 1H); 3.78 (m, 1H); 3.42 (dd, 1H); 3.32-3.14 (m, 2H); 2.20 (m, 1H); 2.00-1.77 (m, 2H); 1.65 (m, 1H).

Example 33

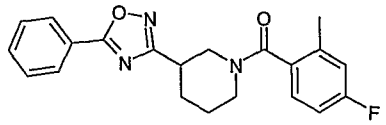
(2,4-Difluoro-phenyl)-[3-(5-phenyl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone



The compound was prepared following the procedure described in the Example 3 (F), using 3-[5-(phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (prepared as described in the Example 26 (B)) and 2,4-difluorobenzoyl chloride. Purification of the final compound was performed by flash chromatography on silica gel (eluent: DCM:MeOH 99:1).
Yield: 78% (white solid); mp:116-117°C; LCMS (RT): 7.27 min (Method E); MS (ES+) gave m/z: 370.1.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.07 (m, 2H); 7.74-7.58 (m, 3H); 7.46 (m, 1H); 7.30-7.06 (m, 2H); 4.58 (m br, 1H); 4.02 (m br, 1H); 3.55-3.07 (m, 3H); 2.21 (m, 1H); 2.01-1.77 (m, 2H); 1.63 (m, 1H).

Example 34

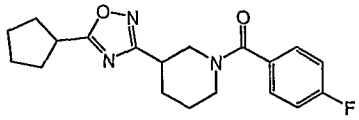
(4-Fluoro-2-methyl-phenyl)-[3-(5-phenyl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone



The compound was prepared following the procedure described in the Example 5, using 4-fluoro-2-methyl-benzoic acid as acid of choice and starting from 3-[5-(phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (prepared as described in the Example 26 (B)). Purification of the final compound was performed by flash chromatography on silica gel (eluent: DCM:MeOH 99:1)
Yield: 78% (pale yellow oil); LCMS (RT): 7.10 min (Method E); MS (ES+) gave m/z: 366.2.
$^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.07 (d, 2H); 7.73-7.58 (m, 3H); 7.22 (dd, 1H); 7.08-6.94 (m, 2H); 4.16 (m br, 1H); 3.71 (m br, 1H); 3.42 (dd, 1H); 3.32-3.07 (m, 2H); 2.25 (s, 3H); 2.21 (m, 1H); 1.96 (m, 1H); 1.84 (m, 1H); 1.62 (m, 1H).

Example 35

(4-Fluoro-phenyl)-[3-(5-cyclopentyl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone



35 (A) 3-(5-Cyclopentyl-[1,2,4]oxadiazol-3-yl)-piperidine-1-carboxylic acid tert-butyl ester

The compound was prepared following the procedure described in the Example 3 (D) using 3-(N-hydroxycarbamimidoyl)-piperidine-1-carboxylic acid tert-butyl ester (prepared as described in Example 3 (C)) and cyclopentanecarboxylic acid. Purification of the final compound was performed by passing the crude through a silica gel cartridge (eluent: DCM:MeOH 99.5:0.5).
Yield: 47% (yellow oil); LCMS (RT): 4.47 min (Method F); MS (ES+) gave m/z: 322.2.

35 (B) 3-(5-Cyclopentyl-[1,2,4]oxadiazol-3-yl)-piperidine hydrochloride

The compound was prepared following the procedure described in the Example 3 (E) starting from 3-(5-cyclopentyl-[1,2,4]oxadiazol-3-yl)-piperidine-1-carboxylic acid tert-butyl ester (prepared as described in Example 35 (A)).
Yield: quantitative (pale yellow oil); LCMS (RT): 3.03 min (Method F); MS (ES+) gave m/z: 222.3.

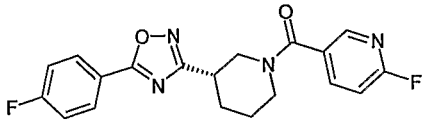
35 (C) (4-Fluoro-phenyl)-[3-(5-cyclopentyl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone

The compound was prepared following the procedure described in the Example 3 (F), using 3-(5-cyclopentyl-[1,2,4]oxadiazol-3-yl)-piperidine hydrochloride (prepared as described in the Example 35 (B)) and 4-fluorobenzoyl chloride. Purification of the

final compound was performed by passing the crude through a silica gel cartridge (eluent: DCM:MeOH 99:1) and successive trituration with pentane.
Yield: 34% (white solid); mp=74-76°C; LCMS (RT): 11.6 min (Method G); MS (ES+) gave m/z: 362.2.
$^1$H-NMR (343 K, DMSO-$d_6$), δ (ppm): 7.51-7.40(m, 2H); 7.25(m, 1H); 4.13(m, 1H); 3.76(m, 1H); 3.45-3.15(m, 3H); 3.07(m, 1H); 2.18-2.00(m, 3H); 1.90-1.52(m, 9H).

Example 36

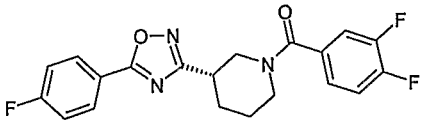
{(S)-3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(6-fluoro-pyridin-3-yl)-methanone



A mixture of (S)-3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (103 mg, 0.36 mmol, prepared as described in the Example 1 (E)), 6-fluoronicotinic acid (61 mg, 0.44 mmol), EDCI.HCl (104 mg, 0.55 mmol), HOBT (82 mg, 0.55 mmol) and TEA (0.102 mL, 0.73 mmol) in dichloromethane (5 mL) was stirred at room temperature for 5h, under nitrogen atmosphere. The solvent was evaporated under reduced pressure. The residue was diluted with water (5 mL) and ethyl acetate (10 mL), the phases were separated and the organic layer was washed with 5% $NaHCO_{3\,(aq)}$ (5 mL x 2 times), then with brine and dried over $Na_2SO_4$. Evaporation of the solvent under reduced pressure gave a crude solid that was purified by flash chromatography (silica gel, eluent: petroleum ether/ethyl acetate 1:1).
{(S)-3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(6-fluoro-pyridin-3-yl)-methanone was obtained as a white solid (104 mg).
Yield: 77% (white solid); mp=103-104°C; $[\alpha]_D^{20}$ = +95.80° (c=0.95, MeOH); LCMS (RT): 7.07 min (Method E); MS (ES+) gave m/z: 371.2.
$^1$H-NMR (373 K, DMSO-$d_6$), δ (ppm): 8.31(d, 1H); 8.12(dd, 2H); 8.00(ddd, 1H); 7.41(dd, 2H); 7.18(dd, 1H); 4.25(dd, 1H); 3.84(ddd, 1H); 3.51(dd, 1H); 3.36(ddd, 1H); 3.24(m, 1H); 2.23(m, 1H); 2.05-1.80(m, 2H); 1.69(m, 1H).

Example 37

(3,4-Difluoro-phenyl)-{(S)-3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone

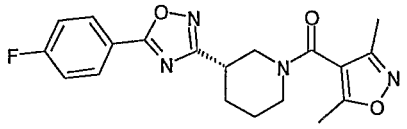


The compound was prepared following the procedure described in the Example 3 (F), using (S)-3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (prepared as described in the Example 1 (E)) and 3,4-difluorobenzoyl chloride. Purification of the final compound was performed by crystallization from diethyl ether.

Yield: 69% (white solid); mp=120°C; $[\alpha]_D^{20}$ = +78.75° (c=0.995, MeOH); LCMS (RT): 8.38 min (Method G); MS (ES+) gave m/z: 388.2.
$^1$H-NMR (343 K, DMSO-$d_6$), δ (ppm): 8.14(dd, 2H); 7.45(m, 2H); 7.44(dd, 2H); 7.27(m, 1H); 4.21(m, 1H); 3.78(m, 1H); 3.41(dd, 1H); 3.26(ddd, 1H); 3.18(m, 1H); 2.20(m, 1H); 1.99-1.76(m, 2H); 1.64(m, 1H).

Example 38

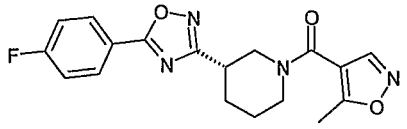
(3,5-Dimethyl-isoxazol-4-yl)-{(S)-3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone



The compound was prepared following the procedure described in the Example 36, using (S)-3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (prepared as described in the Example 1 (E)) and 3,5-dimethyl-isoxazole-4-carboxylic acid. Purification of the final compound was performed by flash chromatography (silica gel, eluent: petroleum ether/ethyl acetate 1:1).
Yield: 67% (white solid); mp=85°C; $[\alpha]_D^{20}$ = +73.65° (c=1.015, MeOH); LCMS (RT): 9.28 min (Method G); MS (ES+) gave m/z: 371.2.
$^1$H-NMR (373 K, DMSO-$d_6$), δ (ppm): 8.14(dd, 2H); 7.41(dd, 2H); 4.18(dd, 1H); 3.75(ddd, 1H); 3.50(dd, 1H); 3.36(ddd, 1H); 3.14(ddd, 1H); 2.37(s, 3H); 2.21(m, 1H); 2.17(s, 3H); 1.97(m, 1H); 1.86(m, 1H); 1.62(m, 1H).

Example 39

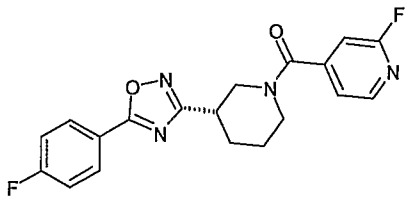
{(S)-3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(5-methyl-isoxazol-4-yl)-methanone



The compound was prepared following the procedure described in the Example 36, using (S)-3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (prepared as described in the Example 1 (E)) and 5-methylisoxazole-4-carboxylic acid. Purification of the final compound was performed by flash chromatography (silica gel, eluent: petroleum ether/ethyl acetate 1:1).
Yield: 69% (white solid); mp=65°C; $[\alpha]_D^{20}$ = +83.11° (c=1.01, MeOH); LCMS (RT): 6.98 min (Method E); MS (ES+) gave m/z: 357.2.
$^1$H-NMR (373 K, DMSO-$d_6$), δ (ppm): 8.50(s, 1H); 8.13(dd, 2H); 7.41(dd, 2H); 4.40(dd, 1H); 3.82(ddd, 1H); 3.47(dd, 1H); 3.32(ddd, 1H); 3.17(m, 1H); 2.48(s, 3H); 2.22(m, 1H); 2.01-1.80(m, 2H); 1.68(m, 1H).

Example 40

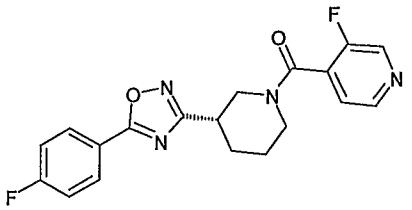
{(S)-3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(2-fluoro-pyridin-4-yl)-methanone



The compound was prepared following the procedure described in the Example 5, using (S)-3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (prepared as described in the Example 1 (E)) and 2-fluoroisonicotinic acid. The title compound was obtained pure after work-up.
Yield: quantitative (white solid); mp=117-119°C; $[\alpha]_D^{20}$ = +74.49° (c=0.52, MeOH); LCMS (RT): 2.93 min (Method H); MS (ES+) gave m/z: 371.2.
$^1$H-NMR (353 K, DMSO-$d_6$), δ (ppm): 8.31(d, 1H); 8.13(dd, 2H); 7.40(dd, 2H); 7.30(dd, 1H); 7.11(d, 1H); 4.19(m br, 1H); 3.76(m br, 1H); 3.46(dd, 1H); 3.30(m, 1H); 3.21(m, 1H); 2.20(m, 1H); 2.00-1.79(m, 2H); 1.69(m, 1H).

Example 41

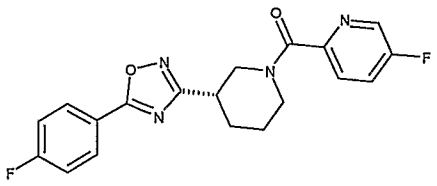
{(S)-3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(3-fluoro-pyridin-4-yl)-methanone



The compound was prepared following the procedure described in the Example 5, using (S)-3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (prepared as described in the Example 1 (E)) and 3-fluoroisonicotinic acid. The title compound was obtained pure after work-up.
Yield: quantitative (gummy yellow solid); $[\alpha]_D^{20}$ = +66.67° (c=0.58, MeOH); LCMS (RT): 2.76 min (Method H); MS (ES+) gave m/z: 371.2.
$^1$H-NMR (373 K, DMSO-$d_6$), δ (ppm): 8.59(s, 1H); 8.49(dd, 1H); 8.12(dd, 2H); 7.41(dd, 2H); 7.41(dd, 1H); 4.19(m br, 1H); 3.76(m br, 1H); 3.50(dd, 1H); 3.35(m, 1H); 3.20(m, 1H); 2.25(m, 1H); 2.06-1.82(m, 2H); 1.69(m, 1H).

Example 42

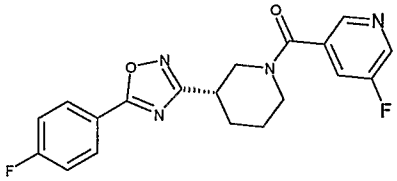
{(S)-3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(5-fluoro-pyridin-2-yl)-methanone



The compound was prepared following the procedure described in the Example 5, using (S)-3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (prepared as described in the Example 1 (E)) and 5-fluoropyridine-2-carboxylic acid. The title compound was obtained pure after purification by flash chromatography (silica gel, eluent: DCM/MeOH/$NH_4OH$ 98/2/0.2) and successive trituration with hexane/diethyl ether 1:1.
Yield: 16% (white powder); mp=93-95°C; LCMS (RT): 2.92 min (Method H); MS (ES+) gave m/z: 371.1.
$^1$H-NMR (353 K, DMSO-$d_6$), δ (ppm): 8.54(s, 1H); 8.13(m, 2H); 7.78(m, 1H); 7.66(m, 1H); 7.44(dd, 2H); 3.97(m br, 1H); 3.44(m br, 1H); 3.28(m, 1H); 3.17(m, 1H); 3.05(m, 1H); 2.23(m, 1H); 2.02-1.77(m, 2H); 1.66(m, 1H).

Example 43

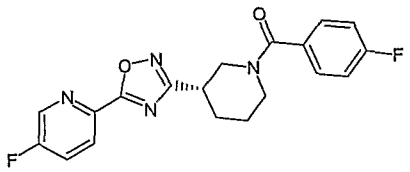
{(S)-3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(5-fluoro-pyridin-3-yl)-methanone



The compound was prepared following the procedure described in the Example 36, using (S)-3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidine hydrochloride (prepared as described in the Example 1 (E)) and 5-fluoropyridine-3-carboxylic acid. The title compound was obtained pure after purification by a first flash chromatography (silica gel, eluent: petroleum ether/ethyl acetate 1:1) and then a second flash chromatography (silica gel, eluent: petroleum ether/ethyl acetate 6:4).
Yield: 43% (gummy white solid); $[\alpha]_D^{20}$ = +79.3° (c=0.99, MeOH); LCMS (RT): 2.81 min (Method I); MS (ES+) gave m/z: 371.2.
$^1$H-NMR (DMSO-$d_6$, 353K), δ (ppm): 8.61 (d, 1H); 8.48 (dd, 1H); 8.13 (dd, 2H); 7.73 (ddd, 1H); 7.43 (dd, 2H); 4.21 (m, 1H); 3.78 (m, 1H); 3.47 (dd, 1H); 3.33 (ddd, 1H); 3.22 (ddd, 1H); 2.22 (m, 1H); 1.96 (m, 1H); 1.84 (m, 1H); 1.69 (m, 1H).

Example 44

(S)-(4-fluorophenyl)-{3-[5-(5-fluoropyridin-2-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone



44 (A) (S)-3-Carbamoyl-piperidine-1-carboxylic acid tert-butyl ester

Triethylamine (1.21 mL, 8.72 mmol) and then ethyl chloroformate (0.8 mL, 8.30 mmol) were added dropwise at 0°C to a solution of (S)-1-Boc-piperidine-3-carboxylic acid (2 g, 8.72 mmol) in chloroform (40 mL), under nitrogen atmosphere. After stirring 10 min at 0°C, $NH_3$ (gas) was bubbled into the solution for 1h. The reaction mixture was then stirred at room temperature for 3h, 5% $NaHCO_3$ (aq) was added and the phases were separated. The organic layer was dried over sodium sulphate and evaporated under reduced pressure to afford the title compound, which was used for the next step without further purification.
Yield: quantitative; LCMS (RT): 3.31 min (Method A); MS (ES+) gave m/z: 229.0.

44 (B) (S)-3-Cyano-piperidine-1-carboxylic acid tert-butyl ester

Phosphorus oxychloride (812 uL, 8.72 mmol) was added dropwise at 0°C to a solution of (S)-3-carbamoyl-piperidine-1-carboxylic acid tert-butyl ester (2 g, 8.72 mmol) in pyridine (20 mL), under nitrogen atmosphere. After stirring overnight at room temperature, ethyl acetate was added and the solution was washed with 10% HCl (2 times). The phases were separated and the organics were dried over sodium sulphate and evaporated to dryness under reduced pressure.
The title compound was used for the next step without further purification.
Yield: quantitative; LCMS (RT): 4.48 min (Method A); MS (ES+) gave m/z: 211.1.

44 (C) (S)-1-(4-Fluoro-benzoyl)-piperidine-3-carbonitrile

(S)-3-Cyano-piperidine-1-carboxylic acid tert-butyl ester (1.5 g, 7.14 mmol), was dissolved in dioxane (15 mL) and 10 mL of 4N HCl (dioxane solution) were added dropwise at 0°C. The resulting mixture was stirred at room temperature for 5h. The solvent was evaporated under reduced pressure to afford (S)-piperidine-3-carbonitrile hydrochloride as a white solid, that was used for the next step without further purification.
To a suspension of (S)-piperidine-3-carbonitrile hydrochloride (7.14 mmol) in dry dichloromethane (100 mL), triethylamine (3 mL, 21.4 mmol) and 4-fluorobenzoyl chloride (930 μL, 7.85 mmol) were added dropwise at 0°C. The reaction mixture was allowed to warm at room temperature and stirred for 3h under nitrogen atmosphere. The solution was then treated with 5% $NaHCO_3$ (50 mL, twice) and the phases were separated. The organic layer was washed with 1N HCl (50 mL) and with brine (50 mL), then was dried over $Na_2SO_4$ and evaporated under reduced pressure. The crude was purified by flash chromatography (silica gel, eluent gradient: from petroleum ether/ethyl acetate 7:3 to petroleum ether/ethyl acetate 1:1) to give 1.01g of the title compound.
Yield: 61% (yellow oil); LCMS (RT): 3.7 min (Method D); MS (ES+) gave m/z: 233.1.

44 (D) (S)-1-(4-Fluoro-benzoyl)-N-hydroxy-piperidine-3-carboxamidine

A solution of (S)-1-(4-fluoro-benzoyl)-piperidine-3-carbonitrile (1.01 g, 4.35 mmol) and aqueous hydroxylamine (50% in water, 1.1 mL, 17.4 mmol) in ethanol (10 mL) was refluxed for 4h. The solvent was evaporated under reduced pressure to afford the title compound (1.15 g) that was used for the next step without further purification.

Yield: quantitative; $^1$H-NMR (DMSO-$d_6$), δ (ppm): 8.61 (s br, 1H); 7.44 (dd, 2H); 7.22 (dd, 2H); 5.12 (s br, 2H); 4.00 (m, 2H); 3.17-2.82 (m, 3H); 2.23 (m, 1H); 1.98 (m, 1H); 1.78-1.55 (m, 2H).

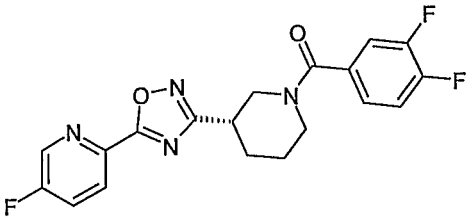
44 (E) (S)-(4-fluorophenyl)-{3-[5-(5-fluoropyridin-2-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone

A mixture of (S)-1-(4-fluoro-benzoyl)-N-hydroxy-piperidine-3-carboxamidine (150 mg, 0.56 mmol), 5-fluoro-pyridine-2-carboxylic acid (79 mg, 0.56 mmol), HOAT (76 mg, 0.56 mmol), EDCI.HCl (163 mg, 0.85 mmol) in dry dioxane (15 mL) was kept under stirring at ambient temperature overnight, under nitrogen atmosphere. The reaction mixture was then heated at 80°C for 5h and the solvent was evaporated under reduced pressure. The residue was diluted with water (40 mL) and ethyl acetate (40 mL), the phases were separated and the organic layer was washed sequentially with water (40 mL, twice), 1N NaOH (40 mL, twice) and with brine. The organic layer was dried over sodium sulphate and the solvent was removed under vacuum to give a residue that was purified by flash chromatography (silica gel, eluent: hexane/ethyl acetate 1:1) and successive preparative HPLC to give the pure title compound (50 mg).

Yield: 24% (White powder); $[\alpha]_D^{20} = +67.5°$ (c=1.0, MeOH); mp=108-110 °C;
LCMS (RT): 2.70 min (Method I); MS (ES+) gave m/z: 371.1.
$^1$H-NMR (DMSO-$d_6$, 353K), δ (ppm): 8.80 (d, 1H); 8.27 (dd, 1H); 7.97 (ddd, 1H); 7.48 (dd, 2H); 7.23 (dd, 2H); 4.25 (m, 1H); 3.83 (m, 1H); 3.43 (dd, 1H); 3.31-3.14 (m, 2H); 2.22 (m, 1H); 1.94 (m, 1H); 1.83 (m, 1H); 1.66 (m, 1H).

Example 45

(S)-(3,4-difluorophenyl)-{3-[5-(5-fluoropyridin-2-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone



45 (A) (S)-3-[5-(5-Fluoro-pyridin-2-yl)-[1,2,4]oxadiazol-3-yl]-piperidine-1-carboxylic acid tert-butyl ester

A mixture of 3-fluoro-pyridine-6-carboxylic acid (0.2 g, 1.43 mmol), HOAT (0.195 g, 1.43 mmol), EDCI.HCl (0.415 g, 2.14 mmol) in dry dioxane (30 mL) was heated at 50°C for 2h, under nitrogen atmosphere, then (S)-3-(N-hydroxycarbamimidoyl)-piperidine-1-carboxylic acid tert-butyl ester (350 mg, 1.43 mmol), prepared as described in Example 1 (C), was added and the reaction mixture was heated at 80°C overnight. The solvent was evaporated under reduced pressure.

The residue was diluted with water (40 mL) and ethyl acetate (40 mL), the phases were separated and the organic layer was washed sequentially with water (40 mL, twice), 1N $Na_2CO_3$ (40 mL, twice) and with brine. The organic layer was dried over sodium sulphate and the solvent was removed under vacuum to give a residue that was purified by flash chromatography (silica gel, eluent gradient: from hexane/ethyl acetate 8:2 to hexane/ethyl acetate 6:4) to give the pure title compound (70 mg).
Yield: 14%; LCMS (RT): 4.3 min (Method A); MS (ES+) gave m/z: 349.0.

45 (B) 5-Fluoro-2-((S)-3-piperidin-3-yl-[1,2,4]oxadiazol-5-yl)-pyridine hydrochloride

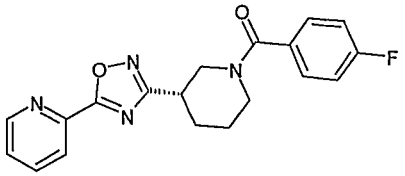
(S)-3-[5-(5-Fluoro-pyridin-2-yl)-[1,2,4]oxadiazol-3-yl]-piperidine-1-carboxylic acid tert-butyl ester (70 mg, 0.2 mmol), was dissolved in DCM (10 mL) and 2 mL of 4N HCl (dioxane solution) were added dropwise at 0°C. The resulting mixture was stirred at room temperature for 3h. The solvent was evaporated under reduced pressure to afford 5-fluoro-2-((S)-3-piperidin-3-yl-[1,2,4]oxadiazol-5-yl)-pyridine hydrochloride (68 mg) as a pale yellow oil, that was used for the next step without further purification.
Yield: quantitative; LCMS (RT): 0.81 min (Method N); MS (ES+) gave m/z: 249.0.

45 (C) (S)-(3,4-difluorophenyl)-{3-[5-(5-fluoropyridin-2-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone

To a suspension of 5-fluoro-2-((S)-3-piperidin-3-yl-[1,2,4]oxadiazol-5-yl)-pyridine hydrochloride (0.20 mmol) in dry dichloromethane (10 mL), triethylamine (45 μL, 0.30 mmol) and 3,4-difluorobenzoyl chloride (35 μL, 0.26 mmol) were added dropwise at 0°C. The reaction mixture was allowed to warm at room temperature and stirred overnight under nitrogen atmosphere. The solvent was removed under reduced pressure. The crude was purified by flash chromatography (silica gel, eluent: hexane/ethyl acetate 1:1) and then by preparative HPLC to give the pure title compound (10 mg) as a white solid.
Yield: 13% (white solid); LCMS (RT): 2.81 min (Method I); MS (ES+) gave m/z: 389.3.
$^1$H-NMR (DMSO-$d_6$, 353K), δ (ppm): 8.79 (d, 1H); 8.27 (dd, 1H); 7.97 (ddd, 1H); 7.51-7.40 (m, 2H); 7.28 (m, 1H); 4.22 (m, 1H); 3.79 (m, 1H); 3.44 (dd, 1H); 3.33-3.17 (m, 2H); 2.23 (m, 1H); 1.95 (m, 1H); 1.84 (m, 1H); 1.66 (m, 1H).

Example 46

(S)-(4-fluorophenyl)-{3-[5-(pyridin-2-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone



46 (A) (S)-3-(5-Pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidine-1-carboxylic acid tert-butyl ester

(S)-3-(5-Pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidine-1-carboxylic acid tert-butyl ester was obtained following the experimental procedure described in Example 45(A), starting from pyridine-2-carboxylic acid and (S)-3-(N-

hydroxycarbamimidoyl)-piperidine-1-carboxylic acid tert-butyl ester. Purification was performed by flash chromatography (silica gel, eluent gradient: from petroleum ether/ethyl acetate 8:2 to petroleum ether /ethyl acetate 7:3) to give the pure title compound.
Yield: 54%; LCMS (RT): 5.31 min (Method D); MS (ES+) gave m/z: 331.1.

46 (B) 2-((S)-3-Piperidin-3-yl-[1,2,4]oxadiazol-5-yl)-pyridine hydrochloride

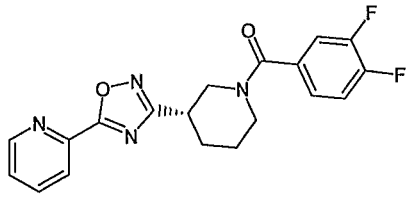
2-((S)-3-Piperidin-3-yl-[1,2,4]oxadiazol-5-yl)-pyridine hydrochloride was obtained following the experimental procedure described in Example 45(B), starting from (S)-3-(5-pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidine-1-carboxylic acid tert-butyl ester.
Yield: quantitative; LCMS (RT): 0.75 min (Method M); MS (ES+) gave m/z: 231.0.

46 (C) (S)-(4-fluorophenyl)-{3-[5-(pyridin-2-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone

(S)-(4-fluorophenyl)-{3-[5-(pyridin-2-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone was obtained following the experimental procedure described in Example 45(C), starting from 2-((S)-3-Piperidin-3-yl-[1,2,4]oxadiazol-5-yl)-pyridine hydrochloride and 4-fluorobenzoyl chloride. Purification was performed by flash chromatography (silica gel, eluent: petroleum ether/ethyl acetate 1:2) to give the pure title compound.
Yield: 67% (White gummy solid); LCMS (RT): 3.14 min (Method I); MS (ES+) gave m/z: 353.5.
$^1$H-NMR (DMSO-$d_6$, 343K), δ (ppm): 8.82 (m, 1H); 8.18 (ddd, 1H); 8.08 (ddd, 1H); 7.69 (m, 1H); 7.48 (dd, 2H); 7.24 (dd, 2H); 4.26 (m, 1H); 3.83 (m, 1H); 3.42 (dd, 1H); 3.30-3.15 (m, 2H); 2.24 (m, 1H); 2.00-1.78 (m, 2H); 1.66 (m, 1H).

Example 47

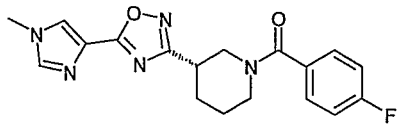
(S)-(3,4-Difluorophenyl)-{3-[5-(pyridin-2-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone




(S)-(3,4-Difluorophenyl)-{3-[5-(pyridin-2-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone was obtained following the experimental procedure described in Example 45(C), starting from 2-((S)-3-piperidin-3-yl-[1,2,4]oxadiazol-5-yl)-pyridine hydrochloride, prepared as described in Example 46 (B), and 3,4-difluorobenzoyl chloride. Purification was performed by flash chromatography (silica gel, eluent: petroleum ether/ethyl acetate 1:2) and successive preparative HPLC to give the pure title compound.
Yield: 15% (colourless gummy solid); LCMS (RT): 2.61 min (Method I); MS (ES+) gave m/z: 371.3.
$^1$H-NMR ($CDCl_3$), δ (ppm): 8.86 (m, 1H); 8.20 (d br, 1H); 7.94 (ddd, 1H); 7.54 (ddd, 1H); 7.31 (m, 1H); 7.21 (m, 2H); 5.18-3.00 (m br, 2H) 3.54 (m, 1H); 3.23 (m, 2H); 2.32 (m, 1H); 2.13-1.89 (m, 2H); 1.71 (m, 1H).

Example 48

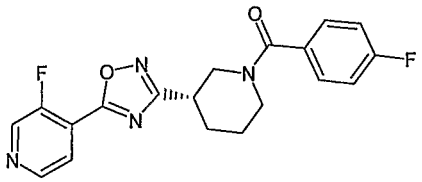
(4-Fluoro-phenyl)-{(S)-3-[5-(1-methyl-1H-imidazol-4-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone



A mixture of 1-methyl-imidazole-4-carboxylic acid (0.15 g, 1.2 mmol), HOAT (0.136 g, 1 mmol), EDCI.HCl (0.192 g, 1 mmol) and triethylamine (400 uL) in dry DCM (10 mL) and DMF (5 mL) was stirred at room temperature for 15 min and then (S)-1-(4-fluoro-benzoyl)-N-hydroxy-piperidine-3-carboxamidine (265 mg, 1 mmol), prepared as described in Example 44 (D), was added. The reaction mixture was stirred at RT for 2h. The mixture was diluted with DCM and washed with 0.2 N NaOH. The solvent was removed and the crude residue was purified by passing it through a silica gel cartridge (eluent gradient: from ethyl acetate to methanol/ethyl acetate 1:9).
The white solid thus obtained was dissolved in acetonitrile (2 mL) and heated in a microwaves oven at 80°C for 1h, then at 95°C for 1h, then at 120°C for 1h. The solvent was removed and the residue was loaded onto a silica gel cartridge (eluent gradient: from ethyl acetate to methanol/ethyl acetate 6:94) to give (4-fluoro-phenyl)-{(S)-3-[5-(1-methyl-1H-imidazol-4-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone as a colourless glass (120 mg).
Yield: 57%; $[\alpha]_D^{20}$ = +86° (c=0.55, MeOH); LCMS (RT): 2.02 min (Method I); MS (ES+) gave m/z: 356.2.
$^1$H-NMR (DMSO-$d_6$, 353K), δ (ppm): 8.01 (d br, 1H); 7.80 (d br, 1H); 7.47 (dd, 2H); 7.23 (dd, 2H); 4.22 (m, 1H); 3.84 (m, 1H); 3.77 (s, 3H); 3.34 (dd, 1H); 3.20 (ddd, 1H); 3.09 (m, 1H); 2.19 (m, 1H); 1.95-1.77 (m, 2H); 1.67 (m, 1H).

Example 49

(4-Fluoro-phenyl)-{(S)-3-[5-(3-fluoro-pyridin-4-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone

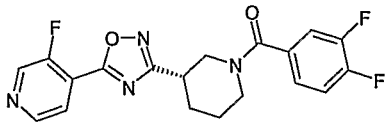


A mixture of 3-fluoro-pyridine-4-carboxylic acid (0.133 g, 0.94 mmol), (S)-1-(4-fluoro-benzoyl)-N-hydroxy-piperidine-3-carboxamidine (250 mg, 0.94 mmol), prepared as described in Example 44 (D), HOBT (0.127 g, 0.94 mmol), EDCI.HCl (0.270 g, 1.41 mmol) and triethylamine (262 µL) in dry dioxane (30 mL) was stirred at room temperature for 4h and then the reaction mixture was heated at 80°C for 4h. The solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography (silica gel, eluent: petroleum ether/ethyl acetate 6:4) to give the pure title compound (146 mg).
Yield: 42%; $[\alpha]_D^{20}$ = +65.5° (c=0.61, MeOH); LCMS (RT): 3.42 min (Method I); MS (ES+) gave m/z: 371.1.

$^1$H-NMR (DMSO-$d_6$, 353K), δ (ppm): 8.88 (d, 1H); 8.71 (dd, 1H); 8.03 (ddd, 1H); 7.48 (dd, 2H); 7.23 (dd, 2H); 4.26 (m, 1H); 3.82 (m, 1H); 3.43 (dd, 1H); 3.26 (m, 2H); 2.24 (m, 1H); 1.98 (m, 1H); 1.85 (m, 1H); 1.66 (m, 1H).

Example 50

(3,4-Difluoro-phenyl)-{(S)-3-[5-(3-fluoro-pyridin-4-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone



50 (A) (S)-1-(3,4-Difluoro-benzoyl)-piperidine-3-carbonitrile

(S)-1-(3,4-Difluoro-benzoyl)-piperidine-3-carbonitrile was obtained following the experimental procedure described in Example 44 (C), using 3,4-difluorobenzoyl chloride as the acylating agent.

The crude was purified by flash chromatography (silica gel, eluent gradient: from petroleum ether/ethyl acetate 7:3 to petroleum ether/ethyl acetate 1:1).

Yield: 18%; LCMS (RT): 4.0 min (Method D); MS (ES+) gave m/z: 251.0.

50 (B) (S)-1-(3,4-Difluoro-benzoyl)-N-hydroxy-piperidine-3-carboxamidine

(S)-1-(3,4-Difluoro-benzoyl)-N-hydroxy-piperidine-3-carboxamidine was obtained following the experimental procedure described in Example 44 (D), starting from (S)-1-(3,4-Difluoro-benzoyl)-piperidine-3-carbonitrile.

LCMS (RT): 1.19 min (Method D); MS (ES+) gave m/z: 284.2.

50 (C) (3,4-Difluoro-phenyl)-{(S)-3-[5-(3-fluoro-pyridin-4-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone

The title compound was obtained following the experimental procedure described in Example 49, starting from (S)-1-(3,4-Difluoro-benzoyl)-N-hydroxy-piperidine-3-carboxamidine and 3-fluoro-pyridine-4-carboxylic acid.

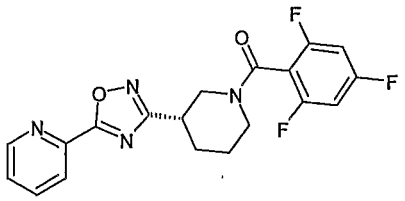
Purification was performed by flash chromatography (silica gel; eluent: petroleum ether/ethyl acetate 6:4).

Yield: 44%; $[\alpha]_D^{20}$ = +60.4° (c=0.55, MeOH); LCMS (RT): 2.78 min (Method I); MS (ES+) gave m/z: 389.1.

$^1$H-NMR (DMSO-$d_6$, 353K), δ (ppm): 8.88 (d, 1H); 8.70 (dd, 1H); 8.02 (dd, 1H); 7.51-7.40 (m, 2H); 7.28 (m, 1H); 4.23 (m, 1H); 3.79 (m, 1H); 3.45 (dd, 1H); 3.35-3.21 (m, 2H); 2.23 (m, 1H); 1.95 (m, 1H); 1.82 (m, 1H); 1.68 (m, 1H).

Example 51

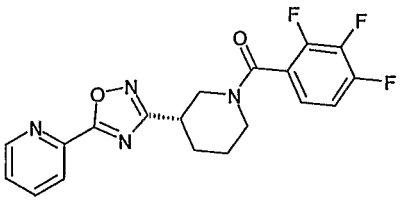
[(S)-3-(5-Pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-(2,4,6-trifluoro-phenyl)-methanone



[(S)-3-(5-Pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-(2,4,6-trifluoro-phenyl)-methanone was obtained following the experimental procedure described in Example 45(C), starting from 2-((S)-3-piperidin-3-yl-[1,2,4]oxadiazol-5-yl)-pyridine hydrochloride, prepared as described in Example 46 (B), and 2,4,6-trifluorobenzoyl chloride. Purification was performed by flash chromatography (silica gel, eluent: petroleum ether/ethyl acetate 1:2) to give the pure title compound.
Yield: 42% (colourless gummy solid); $[\alpha]_D^{20}$ = +68.28° (c=0.63, MeOH); LCMS (RT): 2.68 min (Method I); MS (ES+) gave m/z: 389.2.
$^1$H-NMR (DMSO-$d_6$, 373K), δ (ppm): 8.81 (m, 1H); 8.18 (d br, 1H); 8.06 (ddd, 1H); 7.67 (ddd, 1H); 7.56-7.41 (m, 2H); 4.20 (m br, 1H); 3.72 (m br, 1H); 3.48 (dd, 1H); 3.31 (m, 1H); 3.20 (ddd, 1H); 2.24 (m, 1H); 1.99 (m, 1H); 1.87 (m, 1H); 1.66 (m, 1H).

Example 52

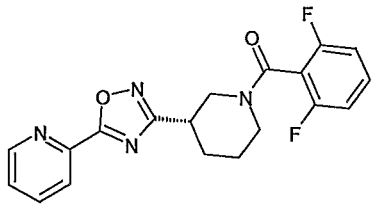
[(S)-3-(5-Pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-(2,3,4-trifluoro-phenyl)-methanone



[(S)-3-(5-Pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-(2,3,4-trifluoro-phenyl)-methanone was obtained following the experimental procedure described in Example 45(C), starting from 2-((S)-3-piperidin-3-yl-[1,2,4]oxadiazol-5-yl)-pyridine hydrochloride, prepared as described in Example 46 (B), and 2,3,4-trifluorobenzoyl chloride. Purification was performed by flash chromatography (silica gel, eluent: petroleum ether/ethyl acetate 1:2) to give the pure title compound.
Yield: 54% (white gummy solid); $[\alpha]_D^{20}$ = +62.9° (c=1.8, MeOH); LCMS (RT): 2.70 min (Method I); MS (ES+) gave m/z: 389.2.
$^1$H-NMR (DMSO-$d_6$, 373K), δ (ppm): 8.81 (ddd, 1H); 8.17 (d br, 1H); 8.07 (ddd, 1H); 7.67 (ddd, 1H); 7.37-7.23 (m, 2H); 4.20 (m br, 1H); 3.75 (m br, 1H); 3.51 (dd, 1H); 3.33 (m, 1H); 3.20 (ddd, 1H); 2.24 (m, 1H); 1.99 (m, 1H); 1.87 (m, 1H); 1.66 (m, 1H).

Example 53

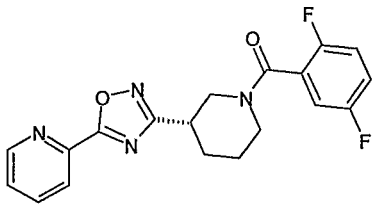
(2,6-Difluoro-phenyl)-[(S)-3-(5-pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone



(2,6-Difluoro-phenyl)-[(S)-3-(5-pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone was obtained following the experimental procedure described in Example 45(C), starting from 2-((S)-3-piperidin-3-yl-[1,2,4]oxadiazol-5-yl)-pyridine hydrochloride, prepared as described in Example 46 (B), and 2,6-difluorobenzoyl chloride. Purification was performed by flash chromatography (silica gel, eluent: petroleum ether/ethyl acetate 1:2) to give the pure title compound.
Yield: 42% (colourless gummy solid); $[\alpha]_D^{20}$ = +70.76° (c=0.52, MeOH); LCMS (RT): 2.53 min (Method I); MS (ES+) gave m/z: 371.3.
$^1$H-NMR (DMSO-$d_6$, 300 MHz, rotamers present), δ (ppm): 8.83 (m, 1H); 8.27 and 8.12 (ddd, 1H); 8.09 (m, 1H); 7.71 (m, 1H); 7.62-7.48 (m, 1H); 7.29-7.19 (m, 1H); 7.23 and 7.04 (dd, 1H); 4.68 (m, 1H); 4.02 (m, 1H); 3.73 and 3.60 (dd, 1H); 3.43 (m, 1H); 3.13 (m, 1H); 2.21 (m, 1H); 2.09-1.77 (m, 2H); 1.73-1.47 (m, 1H).

Example 54

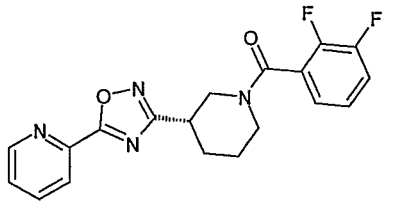
(2,5-Difluoro-phenyl)-[(S)-3-(5-pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone



(2,5-Difluoro-phenyl)-[(S)-3-(5-pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone was obtained following the experimental procedure described in Example 45(C), starting from 2-((S)-3-piperidin-3-yl-[1,2,4]oxadiazol-5-yl)-pyridine hydrochloride, prepared as described in Example 46 (B), and 2,5-difluorobenzoyl chloride. Purification was performed by flash chromatography (silica gel, eluent: petroleum ether/ethyl acetate 1:2) to give the pure title compound.
Yield: 30% (colourless gummy solid); LCMS (RT): 3.27 min (Method L); MS (ES+) gave m/z: 371.3.
$^1$H-NMR (DMSO-$d_6$ ,373K), δ (ppm): 8.81 (ddd, 1H); 8.17 (d br, 1H); 8.06 (ddd, 1H); 7.67 (ddd, 1H); 7.26 (m, 3H); 4.19 (m br, 1H); 3.77 (m br, 1H); 3.47 (dd, 1H); 3.37-3.14 (m, 2H); 2.25 (m, 1H); 1.98 (m, 1H); 1.87 (m, 1H); 1.66 (m, 1H).

Example 55

(2,3-Difluoro-phenyl)-[(S)-3-(5-pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone



(2,3-Difluoro-phenyl)-[(S)-3-(5-pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone was obtained following the experimental procedure described in Example 45(C), starting from 2-((S)-3-piperidin-3-yl-[1,2,4]oxadiazol-5-yl)-pyridine hydrochloride, prepared as described in Example 46 (B), and 2,6-difluorobenzoyl chloride. Purification was performed by flash chromatography (silica gel, eluent: petroleum ether/ethyl acetate 1:2) to give the pure title compound.
Yield: 37% (colourless gummy solid); $[\alpha]_D^{20}$ = +64.76° (c=0.875, MeOH); LCMS (RT): 2.58 min (Method I); MS (ES+) gave m/z: 371.3.
$^1$H-NMR (DMSO-$d_6$, 373K), δ (ppm): 8.81 (ddd, 1H); 8.17 (d br, 1H); 8.06 (ddd, 1H); 7.67 (ddd, 1H); 7.44 (m, 1H); 7.32-7.18 (m, 2H); 4.22 (m br, 1H); 3.76 (m br, 1H); 3.49 (dd, 1H); 3.31 (m, 1H); 3.19 (m, 1H); 2.26 (m, 1H); 2.00 (m, 1H); 1.88 (m, 1H); 1.67 (m, 1H).

PHARMACOLOGY:

The compounds provided in the present invention are positive allosteric modulators of mGluR5. As such, these compounds do not appear to bind to the orthosteric glutamate recognition site, and do not activate the mGluR5 by themselves. Instead, the response of mGluR5 to a concentration of glutamate or mGluR5 agonist is increased when compounds of Formula I are present. Compounds of Formula I are expected to have their effect at mGluR5 by virtue of their ability to enhance the function of the receptor.

## EXAMPLE A

**mGluR5 assay on rat cultured cortical astrocytes**

Under exposure to growth factors (basic fibroblast growth factor, epidermal growth factor), rat cultured astrocytes express group I-Gq coupled mGluR transcripts, namely mGluR5, but none of the splice variants of mGluR1, and as a consequence, a functional expression of mGluR5 receptors (Miller et al. (1995) J. Neurosci. 15:6103-9): The stimulation of mGluR5 receptors with selective agonist CHPG and the full blockade of the glutamate-induced phosphoinositide (PI) hydrolysis and subsequent intracellular calcium mobilization with specific antagonist as MPEP confirm the unique expression of mGluR5 receptors in this preparation.
This preparation was established and used in order to assess the properties of the compounds of the present invention to increase the $Ca^{2+}$ mobilization-induced by

glutamate without showing any significant activity when applied in the absence of glutamate.

**Primary cortical astrocytes culture:**

Primary glial cultures were prepared from cortices of Sprague-Dawley 16 to 19 days old embryos using a modification of methods described by Mc Carthy and de Vellis (1980) J. Cell Biol. 85:890-902 and Miller et al. (1995) J. Neurosci. 15 (9):6103-9. The cortices were dissected and then dissociated by trituration in a sterile buffer containing 5.36 mM KCl, 0.44 mM $NaHCO_3$, 4.17 mM $KH_2PO_4$, 137 mM NaCl, 0.34 mM $NaH_2PO_4$, 1 g/L glucose. The resulting cell homogenate was plated onto poly-D-lysine precoated T175 flasks (BIOCOAT, Becton Dickinson Biosciences, Erembodegem, Belgium) in Dubelcco's Modified Eagle's Medium (D-MEM GlutaMAX™ I, Invitrogen, Basel, Switzerland) buffered with 25 mM HEPES and 22.7 mM $NaHCO_3$, and supplemented with 4.5g/L glucose, 1 mM pyruvate and 15 % fetal bovine serum (FBS, Invitrogen, Basel, Switzerland), penicillin and streptomycin and incubated at 37°C with 5% $CO_2$. For subsequent seeding, the FBS supplementation was reduced to 10 %. After 12 days, cells were subplated by trypsinisation onto poly-D-lysine precoated 384-well plates at a density of 20.000 cells per well in culture buffer.

**$Ca^{2+}$ mobilization assay using rat cortical astrocytes:**

After one day of incubation, cells were washed with assay buffer containing: 142 mM NaCl, 6 mM KCl, 1 mM $Mg_2SO_4$, 1 mM $CaCl_2$, 20 mM HEPES, 1 g/L glucose, 0.125 mM sulfinpyrazone, pH 7.4. After 60 min of loading with 4 μM Fluo-4 (TefLabs, Austin, TX), the cells were washed three times with 50 μl of PBS Buffer and resuspended in 45 μl of assay Buffer. The plates were then transferred to a Fluorometric Imaging Plate Reader (FLIPR, Molecular Devices, Sunnyvale, CA) for the assessment of intracellular calcium flux. After monitoring the baseline fluorescence for 10 s, a solution containing 10μM of representative compound of the present invention diluted in Assay Buffer (15 μl of 4X dilutions) was added to the cell plate in the absence or in the presence of 300 nM of glutamate. Under these experimental conditions, this concentration induces less than 20 % of the maximal response of glutamate and was the concentration used to detect the positive allosteric modulator properties of the compounds from the present invention. The final DMSO concentration in the assay was 0.3 %. In each experiment, fluorescence was then monitored as a function of time for 3 minutes and the data analyzed using Microsoft Excel and GraphPad Prism. Each data point was also measured two times.

The results in Figure 1 represent the effect of 10 μM of Example # 1 on primary cortical mGluR5-expressing cell cultures in the absence or in the presence of 300 nM glutamate. Data are expressed as the percentage of maximal response observed with 30 μM glutamate applied to the cells. Each bar graph is the mean and S.E.M of duplicate data points and is representative of three independent experiments

The results shown in Example A demonstrate that the compounds described in the present invention do not have an effect per se on mGluR5. Instead, when compounds are added together with an mGluR5 agonist such as glutamate, the effect measured is

significantly potentiated compared to the effect of the agonist alone at the same concentration. This data indicates that the compounds of the present invention are positive allosteric modulators of mGluR5 receptors in native preparations.

## EXAMPLE B

**mGluR5 assay on HEK-expressing rat mGluR5**

**Cell culture**

Positive functional expression of HEK-293 cells stably expressing rat mGluR5 receptor was determined by measuring intracellular $Ca^{2+}$ changes using a Fluorometric Imaging Plate Reader (FLIPR, Molecular Devices, Sunnyvale, CA) in response to glutamate or selective known mGluR5 agonists and antagonists. Rat mGluR5 RT-PCR products in HEK-293 cells were sequenced and found 100% identical to rat mGluR5 Genbank reference sequence (NM_017012). HEK-293 cells expressing rmGluR5 were maintained in media containing DMEM, dialyzed Fetal Bovine Serum (10 %), Glutamax™ (2 mM), Penicillin (100 units/ml), Streptomycin (100 µg/ml), Geneticin (100 µg/ml) and Hygromycin-B (40 µg/ml) at 37°C/5%CO2.

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

After one day of incubation, cells were washed with assay buffer containing: 142 mM NaCl, 6 mM KCl, 1 mM $Mg_2SO_4$, 1 mM $CaCl_2$, 20 mM HEPES, 1 g/L glucose, 0.125 mM sulfinpyrazone, pH 7.4. After 60 min of loading with 4 uM Fluo-4 (TefLabs, Austin, TX), the cells were washed three times with 50 µl of PBS Buffer and resuspended in 45 µl of assay Buffer. The plates were then transferred to a Fluorometric Imaging Plate Reader (FLIPR, Molecular Devices, Sunnyvale, CA) for the assessment of intracellular calcium flux. After monitoring the baseline fluorescence for 10 seconds, increasing concentrations of representative compound (from 0.01 to 60 µM) of the present invention diluted in Assay Buffer (15 µl of 4X dilutions) was added to the cell. The final DMSO concentration in the assay was 0.3 %. In each experiment, fluorescence was then monitored as a function of time for 3 minutes and the data analyzed using Microsoft Excel and GraphPad Prism. Each data point was also measured two times.
Under these experimental conditions, this HEK-rat mGluR5 cell line is able to directly detect positive allosteric modulators without the need of co-addition of glutamate or mGluR5 agonist. Thus, DFB, CPPHA and CDPPB, published reference positive allosteric modulators that are inactive in rat cortical astrocytes culture in the absence of added glutamate (Liu et al (2006) Eur. J. Pharmacol. 536:262-268; Zhang et al (2005); J. Pharmacol. Exp. Ther. 315:1212-1219) are activating, in this system, rat mGluR5 receptors.

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

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

allowing determination of $EC_{50}$ values.

The Table 1 below represents the mean $EC_{50}$ obtained from at least three independent experiments of selected molecules performed in duplicate.

**Table 1:**

| EXAMPLE | Ca++ Flux* | EXAMPLE | Ca++ Flux* |
|---|---|---|---|
| 1 | +++ | 29 | +++ |
| 2 | ++ | 30 | + |
| 3 | +++ | 31 | ++ |
| 4 | +++ | 32 | +++ |
| 5 | ++ | 33 | +++ |
| 6 | +++ | 34 | ++ |
| 7 | +++ | 35 | ++ |
| 8 | ++ | 36 | +++ |
| 9 | +++ | 37 | +++ |
| 10 | +++ | 38 | +++ |
| 11 | ++ | 39 | +++ |
| 12 | ++ | 40 | +++ |
| 13 | +++ | 41 | +++ |
| 14 | ++ | 42 | ++ |
| 15 | +++ | 43 | ++ |
| 16 | ++ | 44 | +++ |
| 17 | +++ | 45 | +++ |
| 18 | +++ | 46 | ++ |
| 19 | ++ | 47 | +++ |
| 20 | + | 48 | + |
| 21 | ++ | 49 | ++ |
| 22 | ++ | 50 | ++ |
| 23 | ++ | 51 | +++ |
| 24 | ++ | 52 | +++ |
| 25 | ++ | 53 | ++ |
| 26 | +++ | 54 | +++ |
| 27 | ++ | 55 | ++ |
| 28 | +++ | | |

***Table legend:**

**+: $EC_{50}$ > 10 μM**
**++: 1 μMol <$EC_{50}$ <10 μM**
**+++: $EC_{50}$ <1 μM**

## EXAMPLE C

**mGluR5 binding assay**

Activity of compounds of the invention was examined following a radioligand binding technique using whole rat brain and tritiated 2-methyl-6-(phenylethynyl)-pyridine ( [$^3$H]-MPEP) as a ligand following similar methods than those described in Gasparini et al. (2002) Bioorg. Med. Chem. Lett. 12:407-409 and in Anderson et al. (2002) J. Pharmacol. Exp. Ther. 303 (3) 1044-1051.

**Membrane preparation:**

Cortices were dissected out from brains of 200-300g Sprague-Dawley rats (Charles River Laboratories, L'Arbresle, France). Tissues were homogenized in 10 volumes (vol/wt) of ice-cold 50 mM Hepes-NaOH (pH 7.4) using a Polytron disrupter (Kinematica AG, Luzern, Switzerland) and centrifuged for 30 min at 40,000 g. (4°C). The supernatant was discarded and the pellet washed twice by resuspension in 10 volumes 50 mM HEPES-NaOH. Membranes were then collected by centrifugation and washed before final resuspension in 10 volumes of 20 mM HEPES-NaOH, pH 7.4. Protein concentration was determined by the Bradford method (Bio-Rad protein assay, Reinach, Switzerland) with bovine serum albumin as standard.

**[$^3$H]-MPEP binding experiments:**

Membranes were thawed and resuspended in binding buffer containing 20 mM HEPES-NaOH, 3 mM $MgCl_2$, 3 mM $CaCl_2$, 100 mM NaCl, pH 7.4. Competition studies were carried out by incubating for 1h at 4°C: 3 nM [$^3$H]-MPEP (39 Ci/mmol, Tocris, Cookson Ltd, Bristol, U.K.), 50 μg membrane and a concentration range of 0.003 nM- 30 μM of compounds, for a total reaction volume of 300 μl. The non-specific binding was defined using 30 μM MPEP. Reaction was terminated by rapid filtration over glass-fiber filter plates (Unifilter 96-well GF/B filter plates, Perkin-Elmer, Schwerzenbach, Switzerland) using 4 x 400 μl ice cold buffer using cell harvester (Filtermate, Perkin-Elmer, Downers Grove, USA). Radioactivity was determined by liquid scintillation spectrometry using a 96-well plate reader (TopCount, Perkin-Elmer, Downers Grove, USA).

**Data analysis:**

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

The compounds of this application have $IC_{50}$ values in the range of less than 100 μM. Example # 1 has $IC_{50}$ value of less than 30 μM.

The results shown in Examples A, B and C demonstrate that the compounds described in the present invention are positive allosteric modulators of rat mGluR5 receptors. These compounds are active in native systems and are able to inhibit the binding of the prototype mGluR5 allosteric modulator [$^3$H]-MPEP known to bind remotely from the glutamate binding site into the transmembrane domains of mGluR5 receptors (Malherbe et al (2003) Mol. Pharmacol. 64(4):823-32).

Thus, the positive allosteric modulators provided in the present invention are expected to increase the effectiveness of glutamate or mGluR5 agonists at mGluR5 receptor. Therefore, these positive allosteric modulators are expected to be useful for treatment of various neurological and psychiatric disorders associated with glutamate dysfunction described to be treated herein and others that can be treated by such positive allosteric modulators.

## EXAMPLE D

**Amphetamine model of schizophrenia**

Amphetamine-induced increases in locomotor ambulation are well known and are widely used as a model of the positive symptoms of schizophrenia. This model is based on evidence that amphetamine increases motor behaviors and can induce a psychotic state in humans (Yui et al. (2000) Ann. N.Y. Acad. Sci. 914:1-12). Further, it is well known that amphetamine-induced increases in locomotor activity are blocked by antipsychotics drugs that are effective in the treatment of schizophrenia (Arnt (1995) Eur. J. Pharmacol. 283:55-62). These results demonstrate that locomotor activation induced by amphetamine is a useful model for screening of compounds which may be useful in the treatment of schizophrenia.

**Subjects**: The present studies were performed in accordance with the animal care and use policies of Addex Pharmaceuticals and the laws and directives of Switzerland governing the care and use of animals. Male C57BL6/j mice (20-30 g) 7 weeks of age at the time of delivery were group housed in a temperature and humidity controlled facility on a 12 hour light /dark cycle for at least 7 days before use. Mice had access to food and water ad libitum except during locomotor activity experiments.

**Assessment of locomotor (ambulatory) activity**: The effects of compounds on amphetamine-induced locomotor activation in mice were tested. Locomotor activity of mice was tested in white plastic boxes 35 cm X 35 cm square with walls 40 cm in height. Locomotor activity (ambulations) was monitored by a videotracking system (VideoTrack, Viewpoint, Champagne au Mont d'Or, France) that recorded the ambulatory movements of mice. Mice were naïve to the apparatus prior to testing. On test days, test compounds (10, 30, 50 or 100 mg/kg i.p. (intraperitoneal)) or vehicle were administered 120 minutes before amphetamine (3.0 mg/kg s.c.) or saline injection. Mice were placed into the locomotor boxes immediately after amphetamine or saline vehicle injection and their locomotor activity, defined as the distance traveled in centimeters (cm), was measured for 60 minutes.

**Compound administration**: The test compound was dissolved in a 5% DMSO/20% Tween 80/75% saline vehicle and administered in a volume of 10 ml/kg. Compound-vehicle-treated mice received the equivalent volume of vehicle solution i.p. in the

absence of added compound. D-amphetamine sulfate (Amino AG, Neuenhof, Switzerland) was dissolved in saline and administered at a dose of 3.0 mg/kg s.c. (expressed as the base) in a volume of 10 ml/kg. D-amphetamine-vehicle-treated mice received an equivalent volume of saline vehicle injected s.c.

**Statistical analyses**: Statistical analyses were performed using GraphPad PRISM statistical software (GraphPad, San Diego, CA, USA). Data were analyzed using an unpaired t-test. The significance level was set at $p<0.05$.

**Effect of compounds on amphetamine-induced locomotor activity in mice**
Data from such an experiment using a representative compound is shown in Figure 2.

Figure 2 shows that the representative compound of the invention at a dose of 30 mg/kg ip significantly attenuated the increase in locomotor activity induced by amphetamine during the first 30 minutes of a 60 minute locomotor activity test session ($p < 0.01$, $t = 3.338$, $df = 13$, $n = 7$ for the vehicle-amphetamine group and $n = 8$ for the Example 1-amphetamine group).

**Summary of in vivo data**

The data presented above show that representative example #1 significantly attenuate the hyperlocomotor effects of amphetamine, a widely accepted animal model of schizophrenia. These results support the potential of compounds of Formula I in the treatment of schizophrenia and related disorders.

The compounds of the present invention are allosteric modulators of mGluR5 receptors, they are useful for the production of medications, especially for the prevention or treatment of central nervous system disorders as well as other disorders modulated by this receptor.

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

FORMULATION EXAMPLES

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

1) Tablets

| | |
|---|---|
| Compound of the example 1 | 5 to 50 mg |
| Di-calcium phosphate | 20 mg |
| Lactose | 30 mg |
| Talcum | 10 mg |
| Magnesium stearate | 5 mg |
| Potato starch | ad 200 mg |

In this example, the compound of the example 1 can be replaced by the same amount of any of the described examples 1 to 55.

2) Suspension

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

3) Injectable

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

4) Ointment

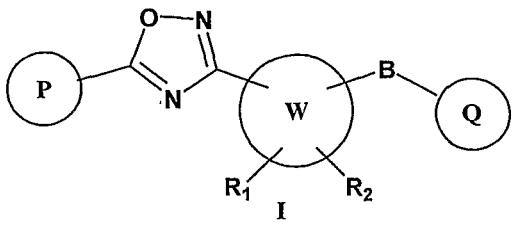
| | |
|---|---|
| Compound of the example 1 | 5 to 1000 mg |
| Stearyl alcohol | 3 g |
| Lanoline | 5 g |
| White petroleum | 15 g |
| Water | ad 100 g |

In this example, the compound 1 can be replaced by the same amount of any of the described examples 1 to 55.

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

Claims:

1. A compound which conforms to the general formula I:



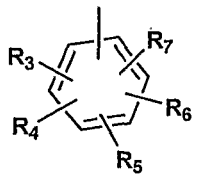

I

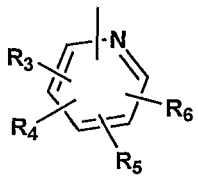
Wherein

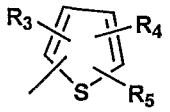
W represents $(C_5-C_7)$cycloalkyl, $(C_3-C_7)$heterocycloalkyl , $(C_3-C_7)$heterocycloalkyl-$(C_1-C_3)$alkyl or $(C_3-C_7)$heterocycloalkenyl ring;

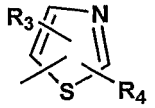
$R_1$ and $R_2$ represent independently hydrogen, -$(C_1-C_6)$alkyl, -$(C_2-C_6)$alkenyl, -$(C_2-C_6)$alkynyl, arylalkyl, heteroarylalkyl, hydroxy, amino, aminoalkyl, hydroxyalkyl, -$(C_1-C_6)$alkoxy or $R_1$ and $R_2$ together can form a $(C_3-C_7)$cycloalkyl ring, a carbonyl bond C=O or a carbon double bond;

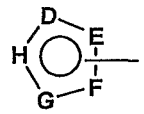
P and Q are each independently selected and denote a cycloalkyl, a heterocycloalkyl, an aryl or heteroaryl group of formula



,


,


,


,



$R_3$, $R_4$, $R_5$, $R_6$, and $R_7$ independently are hydrogen, halogen, -$NO_2$, -$(C_1-C_6)$alkyl, -$(C_3-C_6)$cycloalkyl, -$(C_3-C_7)$cycloalkylalkyl, -$(C_2-C_6)$alkenyl, -$(C_2-C_6)$alkynyl, halo-$(C_1-C_6)$alkyl, heteroaryl, heteroarylalkyl, arylalkyl, aryl, -$OR_8$, -$NR_8R_9$, -$C(=NR_{10})NR_8R_9$, -$NR_8COR_9$, $NR_8CO_2R_9$, $NR_8SO_2R_9$, -$NR_{10}CO\ NR_8R_9$, -$SR_8$, -$S(=O)R_8$, -$S(=O)_2R_8$, -$S(=O)_2NR_8R_9$, -$C(=O)R_8$, -$C(=O)$-O-$R_8$, -$C(=O)NR_8R_9$, -$C(=NR_8)R_9$, or $C(=NOR_8)R_9$ substituents; wherein optionally two substituents are combined to the intervening atoms to form a bicyclic heterocycloalkyl, aryl or heteroaryl ring; wherein each ring is optionally further substituted with 1-5 independent halogen, -CN, -$(C_1-C_6)$alkyl, -O-$(C_0-C_6)$alkyl, -O-$(C_3-C_7)$cycloalkylalkyl, -O(aryl), -O(heteroaryl), -O-(-$C_1-C_3$)alkylaryl, -O-$(C_1-C_3)$alkylheteroaryl, –N((-$C_0-C_6$)alkyl)(($C_0-C_3$)alkylaryl) or –N(($C_0-C_6$)alkyl)(($C_0-C_3$-)alkylheteroaryl) groups;

$R_8$, $R_9$, $R_{10}$ each independently is hydrogen, $(C_1-C_6)$alkyl, $(C_3-C_6)$cycloalkyl, $(C_3-C_7)$cycloalkylalkyl, $(C_2-C_6)$alkenyl, $(C_2-C_6)$alkynyl, halo-$(C_1-C_6)$alkyl, heterocycloalkyl, heteroaryl, heteroarylalkyl, arylalkyl or aryl; any of which is optionally substituted with 1-5

independent halogen, -CN, -($C_1$-$C_6$)alkyl, -O-($C_0$-$C_6$)alkyl, -O-($C_3$-$C_7$)cycloalkylalkyl, -O(aryl), -O(heteroaryl), -N($C_0$-$C_6$-alkyl)$_2$,-N(($C_0$-$C_6$)alkyl)(($C_3$-$C_7$-)cycloalkyl) or –N(($C_0$-$C_6$)alkyl)(aryl) substituents;

D, E, F, G and H represent independently –C($R_3$)=, –C($R_3$)=C($R_4$)-,-C(=O)-,-C(=S)-, –O-, -N=, -N($R_3$)- or -S-;

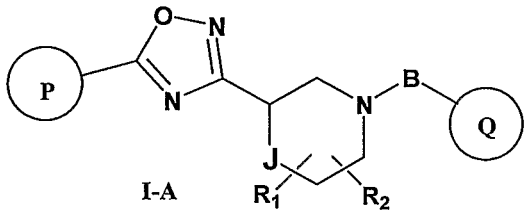
B represents a single bond, -C(=O)-($C_0$-$C_2$)alkyl-, -C(=O)-($C_2$-$C_6$)alkenyl-, -C(=O)-($C_2$-$C_6$)alkynyl-, -C(=O)-O-, -C(=O)N$R_8$-($C_0$-$C_2$)alkyl-, -C(=N$R_8$)N$R_9$-S(=O)-($C_0$-$C_2$)alkyl-, -S(=O)$_2$-($C_0$-$C_2$)alkyl-, -S(=O)$_2$N$R_8$-($C_0$-$C_2$)alkyl-, C(=N$R_8$)-($C_0$-$C_2$)alkyl-, -C(=NO$R_8$)-($C_0$-$C_2$)alkyl- or -C(=NO$R_8$)N$R_9$-($C_0$-$C_2$)alkyl-;

$R_8$ and $R_9$, independently are as defined above;

Any N may be an N-oxide;

or pharmaceutically acceptable salts, hydrates or solvates of such compounds.

2. A compound according to claim 1 having the formula I-A

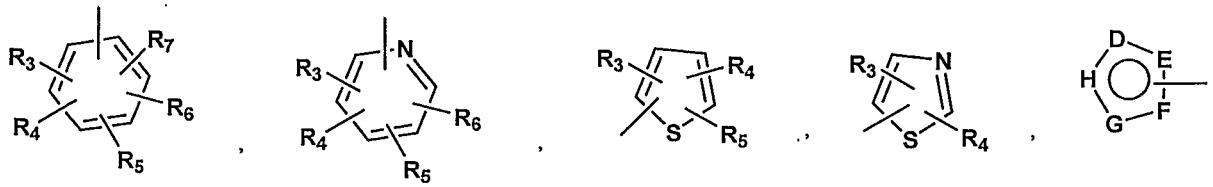



I-A

Wherein

$R_1$ and $R_2$ represent independently hydrogen, -($C_1$-$C_6$)alkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, arylalkyl, heteroarylalkyl, hydroxy, amino, aminoalkyl, hydroxyalkyl, -($C_1$-$C_6$)alkoxy or $R_1$ and $R_2$ together can form a ($C_3$-$C_7$)cycloalkyl ring, a carbonyl bond C=O or a carbon double bond;

P and Q are each independently selected and denote a cycloalkyl, a heterocycloalkyl, an aryl or heteroaryl group of formula




$R_3$, $R_4$, $R_5$, $R_6$, and $R_7$ independently are hydrogen, halogen, -$NO_2$, -($C_1$-$C_6$)alkyl, -($C_3$-$C_6$)cycloalkyl, -($C_3$-$C_7$)cycloalkylalkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, halo-($C_1$-$C_6$)alkyl, heteroaryl, heteroarylalkyl, arylalkyl, aryl, -O$R_8$, -N$R_8$$R_9$, -C(=N$R_{10}$)N$R_8$$R_9$, -N$R_8$CO$R_9$, N$R_8$C$O_2$$R_9$, N$R_8$S$O_2$$R_9$, -N$R_{10}$CO N$R_8$$R_9$, -S$R_8$, -S(=O)$R_8$, -S(=O)$_2$$R_8$, -S(=O)$_2$N$R_8$$R_9$, -C(=O)$R_8$, -C(=O)-O-$R_8$, -C(=O)N$R_8$$R_9$, -

$C(=NR_8)R_9$, or $C(=NOR_8)R_9$ substituents; wherein optionally two substituents are combined to the intervening atoms to form a bicyclic heterocycloalkyl, aryl or heteroaryl ring; wherein each ring is optionally further substituted with 1-5 independent halogen, -CN, -($C_1$-$C_6$)alkyl, -O-($C_0$-$C_6$)alkyl, -O-($C_3$-$C_7$)cycloalkylalkyl, -O(aryl), -O(heteroaryl), -O-(-$C_1$-$C_3$)alkylaryl, -O-($C_1$-$C_3$)alkylheteroaryl, –N((-$C_0$-$C_6$)alkyl)(($C_0$-$C_3$)alkylaryl) or –N(($C_0$-$C_6$)alkyl)(($C_0$-$C_3$-)alkylheteroaryl) groups;

$R_8$, $R_9$, $R_{10}$ each independently is hydrogen, ($C_1$-$C_6$)alkyl, ($C_3$-$C_6$)cycloalkyl, ($C_3$-$C_7$)cycloalkylalkyl, ($C_2$-$C_6$)alkenyl, ($C_2$-$C_6$)alkynyl, halo-($C_1$-$C_6$)alkyl, heterocycloalkyl, heteroaryl, heteroarylalkyl, arylalkyl or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -($C_1$-$C_6$)alkyl, -O-($C_0$-$C_6$)alkyl, -O-($C_3$-$C_7$)cycloalkylalkyl, -O(aryl), -O(heteroaryl), -N($C_0$-$C_6$-alkyl)$_2$,-N(($C_0$-$C_6$)alkyl)(($C_3$-$C_7$-)cycloalkyl) or –N(($C_0$-$C_6$)alkyl)(aryl) substituents;

D, E, F, G and H represent independently –C($R_3$)=, –C($R_3$)=C($R_4$)-,-C(=O)-,-C(=S)-, –O-, -N=, -N($R_3$)- or -S-;

B represents a single bond, -C(=O)-($C_0$-$C_2$)alkyl-, -C(=O)-($C_2$-$C_6$)alkenyl-, -C(=O)-($C_2$-$C_6$)alkynyl-, -C(=O)-O-, -C(=O)N$R_8$-($C_0$-$C_2$)alkyl-, -C(=N$R_8$)N$R_9$-S(=O)-($C_0$-$C_2$)alkyl-, -S(=O)$_2$-($C_0$-$C_2$)alkyl-, -S(=O)$_2$N$R_8$-($C_0$-$C_2$)alkyl-, C(=N$R_8$)-($C_0$-$C_2$)alkyl-, -C(=NO$R_8$)-($C_0$-$C_2$)alkyl- or -C(=NO$R_8$)N$R_9$-($C_0$-$C_2$)alkyl-;

$R_8$ and $R_9$, independently are as defined above;

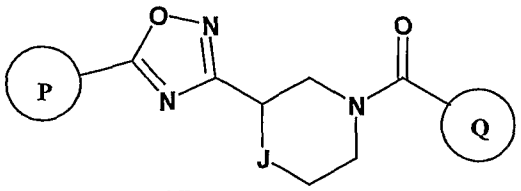
J represents a single bond, –C($R_{11}$)( $R_{12}$), -O-, -N($R_{11}$)- or -S-;

$R_{11}$, $R_{12}$ independently are hydrogen, -($C_1$-$C_6$)alkyl, -($C_3$-$C_6$)cycloalkyl, -($C_3$-$C_7$)cycloalkylalkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, halo($C_1$-$C_6$)alkyl, heteroaryl, heteroarylalkyl, arylalkyl or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -($C_1$-$C_6$)alkyl, -O($C_0$-$C_6$)alkyl, -O($C_3$-$C_7$)cycloalkylalkyl, -O(aryl), -O(heteroaryl), -N(($C_0$-$C_6$)alkyl)(($C_0$-$C_6$)alkyl),-N(($C_0$-$C_6$)alkyl)(($C_3$-$C_7$)cycloalkyl) or –N(($C_0$-$C_6$)alkyl)(aryl) substituents;

Any N may be an N-oxide;

or pharmaceutically acceptable salts, hydrates or solvates of such compounds.

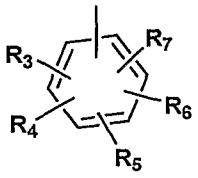
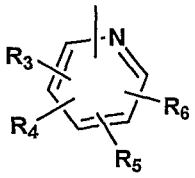
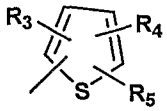
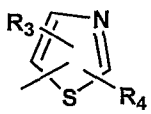
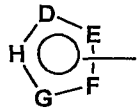
3. A compound according to claim 1 or 2 having the formula I-B



I-B

Wherein

P and Q are each independently selected and denote a cycloalkyl, a heterocycloalkyl, an aryl or heteroaryl group of formula

$R_3$, $R_4$, $R_5$, $R_6$, and $R_7$ independently are hydrogen, halogen, $-NO_2$, $-(C_1-C_6)$alkyl, $-(C_3-C_6)$cycloalkyl, $-(C_3-C_7)$cycloalkylalkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, halo-$(C_1-C_6)$alkyl, heteroaryl, heteroarylalkyl, arylalkyl, aryl, $-OR_8$, $-NR_8R_9$, $-C(=NR_{10})NR_8R_9$, $-NR_8COR_9$, $NR_8CO_2R_9$, $NR_8SO_2R_9$, $-NR_{10}CO\ NR_8R_9$, $-SR_8$, $-S(=O)R_8$, $-S(=O)_2R_8$, $-S(=O)_2NR_8R_9$, $-C(=O)R_8$, $-C(=O)-O-R_8$, $-C(=O)NR_8R_9$, $-C(=NR_8)R_9$, or $C(=NOR_8)R_9$ substituents; wherein optionally two substituents are combined to the intervening atoms to form a bicyclic heterocycloalkyl, aryl or heteroaryl ring; wherein each ring is optionally further substituted with 1-5 independent halogen, -CN, $-(C_1-C_6)$alkyl, $-O-(C_0-C_6)$alkyl, $-O-(C_3-C_7)$cycloalkylalkyl, -O(aryl), -O(heteroaryl), $-O-(-C_1-C_3)$alkylaryl, $-O-(C_1-C_3)$alkylheteroaryl, $-N((-C_0-C_6)$alkyl$)((C_0-C_3)$alkylaryl) or $-N((C_0-C_6)$alkyl$)((C_0-C_3-)$alkylheteroaryl) groups;

$R_8$, $R_9$, $R_{10}$ each independently is hydrogen, $-(C_1-C_6)$alkyl, $-(C_3-C_6)$cycloalkyl, $-(C_3-C_7)$cycloalkylalkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, halo-$(C_1-C_6)$alkyl, heterocycloalkyl, heteroaryl, heteroarylalkyl, arylalkyl or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, $-(C_1-C_6)$alkyl, $-O-(C_0-C_6)$alkyl, $-O-(C_3-C_7)$cycloalkylalkyl, -O(aryl), -O(heteroaryl), $-N(C_0-C_6$-alkyl$)_2$,-$N((C_0-C_6)$alkyl$)((C_3-C_7-)$cycloalkyl) or $-N((C_0-C_6)$alkyl$)$(aryl) substituents;

D, E, F, G and H represent independently $-C(R_3)=$, $-C(R_3)=C(R_4)-$,-C(=O)-,-C(=S)-, –O-, -N=, $-N(R_3)-$ or -S-;

J represents a single bond, $-C(R_{11})(R_{12})$, -O-, $-N(R_{11})$- or -S-;

$R_{11}$, $R_{12}$ independently are hydrogen, -($C_1$-$C_6$)alkyl, -($C_3$-$C_6$)cycloalkyl, -($C_3$-$C_7$)cycloalkylalkyl, -($C_2$-$C_6$)alkenyl, -($C_2$-$C_6$)alkynyl, halo($C_1$-$C_6$)alkyl, heteroaryl, heteroarylalkyl, arylalkyl or aryl; any of which is optionally substituted with 1-5 independent halogen, -CN, -($C_1$-$C_6$)alkyl, -O($C_0$-$C_6$)alkyl, -O($C_3$-$C_7$)cycloalkylalkyl, -O(aryl), -O(heteroaryl), -N(($C_0$-$C_6$)alkyl)(($C_0$-$C_6$)alkyl),-N(($C_0$-$C_6$)alkyl)(($C_3$-$C_7$)cycloalkyl) or –N(($C_0$-$C_6$)alkyl)(aryl) substituents;

Any N may be an N-oxide;

or pharmaceutically acceptable salts, hydrates or solvates of such compounds.

4. A compound according to claims 1 to 3, which can exist as optical isomers, wherein said compound is either the racemic mixture or an individual optical isomer.

5. A compound according to claims 1 to 4, wherein said compounds are selected from:
(4-Fluoro-phenyl)-{(S)-3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
(4-Fluoro-phenyl)-{(R)-3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
(3,4-Difluoro-phenyl)-{3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
(2,4-Difluoro-phenyl)-{3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
(4-Fluoro-2-methylamino-phenyl)-{3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
{3-[5-(2-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(5-fluoro-pyridin-2-yl)-methanone
{3-[5-(2-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(5-methyl-isoxazol-4-yl)-methanone
(4-Fluoro-phenyl)-[3-(5-thiazol-4-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
{3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(6-fluoro-pyridin-3-yl)-methanone
(3,4-Difluoro-phenyl)-{3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
(4-Fluoro-phenyl)-[3-(5-pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
(6-Fluoro-pyridin-3-yl)-[3-(5-pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
{3-[5-(2,4-Difluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(4-fluoro-phenyl)-methanone
(4-Fluoro-phenyl)-[3-(5-pyridin-4-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
(3,4-Difluoro-phenyl)-[3-(5-pyridin-4-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone

(2,4-Difluoro-phenyl)-[3-(5-pyridin-4-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
(3,4-Difluoro-phenyl)-{3-[5-(2,4-difluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
(2,4-Difluoro-phenyl)-{3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
(2,4-Difluoro-phenyl)-{3-[5-(2,4-difluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
(5-Methyl-isoxazol-4-yl)-[3-(5-pyridin-4-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
(6-Fluoro-pyridin-3-yl)-[3-(5-pyridin-4-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
(4-Fluoro-2-methyl-phenyl)-[3-(5-pyridin-4-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
(4-Fluoro-2-methyl-phenyl)-{3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
{3-[5-(2,4-Difluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(5-methyl-isoxazol-4-yl)-methanone
{3-[5-(2,4-Difluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(6-fluoro-pyridin-3-yl)-methanone
(4-Fluoro-phenyl)-[3-(5-phenyl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
(4-Fluoro-2-methyl-phenyl)-{3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
{3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(5-methyl-isoxazol-4-yl)-methanone
(6-Fluoro-pyridin-3-yl)-[3-(5-phenyl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
(6-Fluoro-pyridin-3-yl)-[3-(5-thiazol-4-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
{3-[5-(2,4-Difluoro-phenyl)-[1,2,4] oxadiazol-3-yl]-piperidin-1-yl}-(4-fluoro-2-methyl-phenyl)-methanone
(3,4-Difluoro-phenyl)-[3-(5-phenyl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
(2,4-Difluoro-phenyl)-[3-(5-phenyl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
(4-Fluoro-2-methyl-phenyl)-[3-(5-phenyl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
(4-Fluoro-phenyl)-[3-(5-cyclopentyl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
{(S)-3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(6-fluoro-pyridin-3-yl)-methanone
(3,4-Difluoro-phenyl)-{(S)-3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
(3,5-Dimethyl-isoxazol-4-yl)-{(S)-3-[5-(4-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
{(S)-3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(5-methyl-isoxazol-4-yl)-methanone
{(S)-3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(2-fluoro-pyridin-4-yl)-methanone
{(S)-3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(3-fluoro-pyridin-4-yl)-methanone

{(S)-3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(5-fluoro-pyridin-2-yl)-methanone
{(S)-3-[5-(4-Fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-(5-fluoro-pyridin-3-yl)-methanone
(S)-(4-fluorophenyl)-{3-[5-(5-fluoropyridin-2-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
(S)-(3,4-difluorophenyl)-{3-[5-(5-fluoropyridin-2-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
(S)-(4-fluorophenyl)-{3-[5-(pyridin-2-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
(S)-(3,4-difluorophenyl)-{3-[5-(pyridin-2-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
(4-Fluoro-phenyl)-{(S)-3-[5-(1-methyl-1H-imidazol-4-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
(3,4-Difluoro-phenyl)-{(S)-3-[5-(3-fluoro-pyridin-4-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
(4-Fluoro-phenyl)-{(S)-3-[5-(3-fluoro-pyridin-4-yl)-[1,2,4]oxadiazol-3-yl]-piperidin-1-yl}-methanone
[(S)-3-(5-Pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-(2,4,6-trifluoro-phenyl)-methanone
[(S)-3-(5-Pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-(2,3,4-trifluoro-phenyl)-methanone
(2,6-Difluoro-phenyl)-[(S)-3-(5-pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
(2,5-Difluoro-phenyl)-[(S)-3-(5-pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone
(2,3-Difluoro-phenyl)-[(S)-3-(5-pyridin-2-yl-[1,2,4]oxadiazol-3-yl)-piperidin-1-yl]-methanone.

6. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claims 1 to 5 and a pharmaceutically acceptable carrier and/or excipient.

7. A method of treating or preventing a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of mGluR5 allosteric modulators, comprising administering to a mammal in need of such treatment or prevention, an effective amount of a compound/composition according to claims 1 to 6.

8. A method of treating or preventing a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of mGluR5 positive allosteric modulators (enhancer), comprising administering to a mammal in need of such treatment or prevention, an effective amount of a compound/composition according to claims 1 to 6.

9. A method useful for treating or preventing central nervous system disorders selected from the group consisting of anxiety disorders: Agoraphobia, Generalized Anxiety Disorder (GAD), Obsessive-Compulsive Disorder (OCD), Panic Disorder, Posttraumatic Stress Disorder (PTSD), Social Phobia, Other Phobias,

Substance-Induced Anxiety Disorder, comprising administering an effective amount of a compound/composition according to claims 1 to 6.

10. A method useful for treating or preventing central nervous system disorders selected from the group consisting of childhood disorders: Attention-Deficit/Hyperactivity Disorder), comprising administering an effective amount of a compound/composition according to claims 1 to 6.

11. A method useful for treating or preventing central nervous system disorders selected from the group consisting of eating Disorders (Anorexia Nervosa, Bulimia Nervosa), comprising administering an effective amount of a compound/composition according to claims 1 to 6.

12. A method useful for treating or preventing central nervous system disorders selected from the group consisting of mood disorders: Bipolar Disorders (I & II), Cyclothymic Disorder, Depression, Dysthymic Disorder, Major Depressive Disorder, Substance-Induced Mood Disorder, comprising administering an effective amount of a compound/composition according to claims 1 to 6.

13. A method useful for treating or preventing central nervous system disorders selected from the group consisting of psychotic disorders: Schizophrenia, Delusional Disorder, Schizoaffective Disorder, Schizophreniform Disorder, Substance-Induced Psychotic Disorder, comprising administering an effective amount of a compound/composition according to claims 1 to 6.

14. A method useful for treating or preventing central nervous system disorders selected from the group consisting of cognitive disorders: Delirium, Substance-Induced Persisting Delirium, Dementia, Dementia Due to HIV Disease, Dementia Due to Huntington's Disease, Dementia Due to Parkinson's Disease, Dementia of the Alzheimer's Type, Substance-Induced Persisting Dementia, Mild Cognitive Impairment, comprising administering an effective amount of a compound/composition according to claims 1 to 6.

15. A method useful for treating or preventing central nervous system disorders selected from the group consisting of personality disorders: Obsessive-Compulsive Personality Disorder, Schizoid, Schizotypal disorder, comprising administering an effective amount of a compound/composition according to claims 1 to 6.

16. A method useful for treating or preventing central nervous system disorders selected from the group consisting of substance-related disorders: Alcohol abuse, Alcohol dependence, Alcohol withdrawal, Alcohol withdrawal delirium, Alcohol-induced psychotic disorder, Amphetamine dependence, Amphetamine withdrawal, Cocaine dependence, Cocaine withdrawal, Nicotine dependence, Nicotine withdrawal, Opioid dependence, Opioid withdrawal, comprising administering an effective amount of a compound/composition according to claims 1 to 6.

17. A method useful for treating or preventing inflammatory central nervous system disorders selected from multiple sclerosis form such as benign multiple sclerosis, relapsing-remitting multiple sclerosis, secondary progressive multiple

sclerosis, primary progressive multiple sclerosis, progressive-relapsing multiple sclerosis, comprising administering an effective amount of a compound/composition according to claims 1 to 6.

18. Use of a compound according to claims 1 to 6 in the manufacture of a medicament for a treatment or prevention as defined in any of claims 9 to 17.

19. The use of the compounds of the invention to prepare tracers for imaging metabotropic glutamate receptors.