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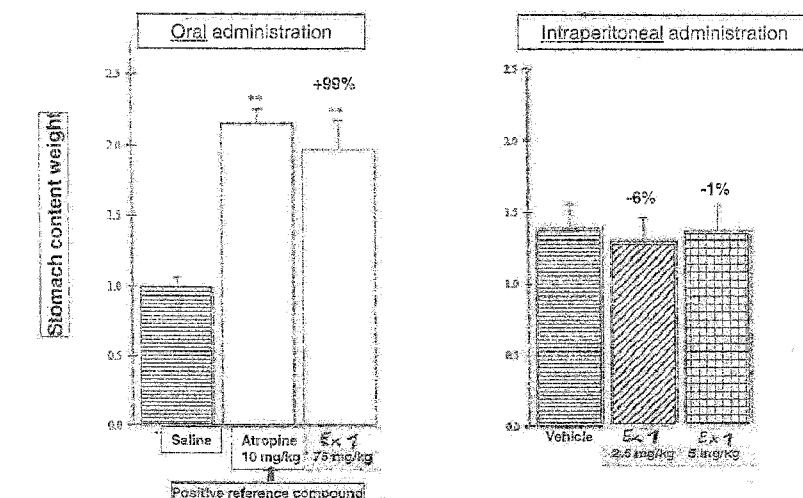
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[Continued on next page]

(54) Title: ENTERIC FORMULATIONS OF METABOTROPIC GLUTAMATE RECEPTOR MODULATORS

Fig. 1

Gastric emptying after oral and intraperitoneal administration



(57) Abstract: A pharmaceutical formulation comprising at least one negative allosteric modulator of the mGluR5 receptor and at least one pharmaceutically acceptable excipient in the form of an enteric tablet, enteric capsule or multiple unit dosage form has improved activity for the treatment of Parkinson's disease.



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— *with international search report (Art. 21(3))*

Enteric formulations of metabotropic glutamate receptor modulators

- 5 The present invention relates to enteric formulations of metabotropic glutamate receptor (mGluR) modulators, methods for the preparation and testing of these formulations and a medicament for use for the treatment of various diseases, such as neurological disorders and in particular Parkinson disease.
- 10 Neuronal stimuli are transmitted by the central nervous system (CNS) through the interaction of neurotransmitters released by neurons. The neurotransmitters have a specific effect on neuroreceptors of other neurons. L-glutamic acid is a major excitatory neurotransmitter in the mammalian CNS and plays a critical role in a large number of physiological processes. Glutamate-dependent stimulus receptors are divided into two
- 15 main groups. The first group comprises ligand-controlled ion-channels, the other comprises metabotropic glutamate receptors (mGluR). Metabotropic glutamate receptors are a subfamily of the G-protein-coupled receptors (GPCR). Eight different members of these mGluR are known and various medical applications have been described. On the basis of structural parameters such as sequence homology, the second messenger system utilized by
- 20 the receptors and their different affinity to low-molecular weight compounds, these eight receptors can be divided into three groups (I, II and III).

MGluR1 and mGluR5 belong to Group I which are positively coupled to phospholipase C and their activation leads to a mobilization of intracellular calcium ions. MGluR2 and

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

The mGluR5 modulators, which are of particular interest for the present invention, have

30 been shown to modulate the effects of the pre-synaptically released neurotransmitter glutamate via postsynaptic mechanisms. The modulators can be positive and/or negative mGluR5 modulators. The modulators may increase or inhibit the effects mediated through these metabotropic glutamate receptors. The invention relates to enteric (coated) formulations, in particular to formulations of different types of negative allosteric

35 modulators of the mGluR5 receptor. Of particular interest are oral formulations of negative

mGluR5 modulators. Such modulators decrease the effects mediated through metabotropic glutamate receptors.

A variety of patho-physiological processes and disease states affecting the CNS are related to abnormal glutamate neurotransmission. As mGluR5 receptors are expressed in several areas of the CNS, the negative modulators, if applied in an appropriate formulation, are therapeutically beneficial in the treatment of several CNS diseases.

The present invention relates to a pharmaceutical formulation, comprising at least one negative allosteric modulator of the mGluR5 receptor and at least one layer of enteric coating (or at least one enteric polymer), where the components of the enteric coating (formulation) are specifically chosen that the pharmaceutical formulation releases the negative allosteric modulator of the mGluR5 receptor in the small and/or large intestine.

Several of these negative allosteric modulators of the mGluR5 receptor have been described in the literature, e. g. the compounds 2-methyl-6-phenylethynyl-pyridine (MPEP), 1-methyl-6-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and several substituted pyrazolopyrimidine derivatives. Some of these heterocyclic compounds are easily dissolvable in water, but often the compounds have a low solubility in water.

US 2003/0059471 describe solid formulations comprising a plurality of discrete, flat flakes containing a drug compound. The drug compound can be of various classes. Some CNS-compounds are mentioned, e.g. the drug compound Fenobam.

The application routes of negative allosteric modulators of the mGluR5 receptor can be e.g. the pulmonary, rectal, parenteral, nasal, otological, buccal, dermal and/or oral or a combination of several of these application routes. As the treatment with modulators of the mGluR5 receptor for the related diseases often is a long lasting therapy and because often larger amounts of active substance or combinations of substances are used, the oral application route is preferred and has a high compliance and acceptance by patients. The mGluR5 receptor concentration or the distribution of the receptors varies in different parts of the gastro-intestinal tract. Stimulation of these receptors causes interference with the biological movement process of the gastro-intestinal tract and more generally with the digestion process. Negative allosteric modulators of the mGluR5 receptor can e.g. slow down the digestion or lead to a highly variable digestion process.

Some modulator compounds also have a limited stability in an acidic environment (e. g. in the stomach) or do not achieve a good level of bioavailability if applied by immediate

release oral formulation. The term bioavailability describes the percentage of an active substance that is adsorbed in a defined period of time in the blood compared with the dose administered via the oral route.

5 Oral administration of a pharmaceutical product often exposes the active substance to a wide range of influences that may alter the compound. The intestinal flora, various enzymes and food components are among the factors which affect the chemical consistency, the gastrointestinal transport rate and/or the absorption rate of the compound applied. The bioavailability is improved by the specific formulation of the modulator
10 compounds. An oral formulation of a modulator of the mGluR5 receptor is transported into the intestine via the stomach, passing through very different physiological environments. For example, the pH value changes from 1 to 3 in the stomach to 5 to 7 in the duodenum and then to 7 to 9 in the ileum. Further, the specific surface area alters from the stomach to the small intestine, where absorption can occur. Before entering the intestine, the
15 pharmaceutical formulation of a modulator of the mGluR5 receptor is exposed to high proton concentration, which can cause hydrolysis, flocculation and precipitation. Furthermore, the time, quantity and type of food consumed and the level of disease of the patient can determine the speed at which the active substance enters and leaves the intestine. The available concentration of the modulator of the mGluR5 receptor in the
20 blood can therefore vary depending on the type of formulation administered.

By using standard immediate release oral formulations, the modulator of the mGluR5 receptor, or at least a part of the drug substance comes in contact with the stomach surface and can elicit effects like slowing down the emptying of the stomach by interaction with
25 local gastric receptors. In order to minimise the interaction of the drug substance with these receptors in the animal or human stomach, the release of the active substance can be directed in the small or large intestine. For the targeted release according to this invention, several formulation technologies can be applied. One particularly formulation technology for delayed release is the preparation of enteric formulations (or enteric coated
30 formulations), such as coated tablets or coated capsules.

Enteric formulation in this context means in particular, that a composition (e.g. tablet or capsule) comprising the modulator of the mGluR5 receptor is combined with, e. g. coated, with a material that permits a transit of the active substance through the (acidic) stomach
35 with only limited or without any release of drug substance in the stomach. The active substance is transported into the intestine or into a special part of the intestine before the active substance is released at a pH of 6.8 or higher. The term "enteric" means in particular that the release of the active substance is triggered either in the small intestine or in the

large intestine or in both compartments. The selection of the optimal release site depends on the type of disease, the intended plasma peak concentrations, the intended plasma time/concentration-profile and the intended time/concentration profile at the target site of action for the respective active substance.

5

The term "capsule" encompasses a pharmaceutically acceptable formulation enclosing a dose of one active substance or a combination of active substances and one excipient or a combination of excipients, which is covered by a polymer shell, which e. g. basically consists of gelatine, starch or cellulose or chemical derivatives and combinations of these polymers. Capsules can be, depending on their consistency, soft or hard capsules. Their content can be solid, semi solid or liquid.

The term "excipient" defines a pharmaceutically and/or pharmacologically inactive substance, which passes defined characteristics with relevance for the formulation or the drug product. The term "excipient" also encompasses a pharmaceutically acceptable, pharmacologically inactive ingredient such as e. g. a binder, a filler, a coating-forming compound, a plasticizers for coatings and a compound which masks odors. Examples of optional excipients are pigments, flavors, sweeteners, opacifiers, anti-adhesives, preservatives, glidants, lubricants and sorbents. Suitable substances are known in the art. The term "excipient" applied to pharmaceutical formulations of the invention also refers to a diluent or vehicle with which an active substance is administered. Such pharmaceutical excipient can be from animal, vegetable or synthetic origin, see also A.R. Gennaro, 20th Edition in "Remington: The Science and Practice of Pharmacy".

The term "granule" encompasses aggregates of particles, e.g. powder particles, to form a multi-particle entity. In pharmaceutical terms, a granule encompasses small particles gathered into a larger, permanent aggregate in which the original particles may still be identified. Granules may be obtained in a granulation process in which powder particles adhere to each other by different physical mechanisms. Processes such as thermoplastic granulation, aqueous or organic solvent based pot granulation, granulation in a tumbling mixer, granulation in a fluidized bed granulator, granulation by spray drying or dry granulation by compaction are known in the field of pharmaceutical compositions.

The term "immediate release" defines a release rate in which at least 80 % of the active substance is released after 30 minutes after oral application of the formulation. Experimental conditions for measuring the release are the conditions as defined in U.S. Pharmacopoeia, e.g. USP 34, or European Pharmacopoeia, e.g. EP 7.

Contrary to this, the term “delayed release formulation” encompasses a dosage form from which releases an incorporated active substance in a timely delayed and/or controlled way and/or rapidly or slowly and in a defined part of the gastro intestinal tract over a period of time as defined in detail. This term encompasses a pharmaceutical formulation comprising a therapeutically effective amount of the active substance (or a pharmaceutically acceptable salt, solvate, polymorphic form or isomer thereof), and at least one release delaying excipient. The term encompasses an enteric coating formulation which may be orally administered to a patient in need thereof.

10 The term “multiple unit dosage form” encompasses a formulation which consists of at least two units which contain the effective amount of the mGLuR5 modulator. The term “single unit dosage form” encompasses a formulation which consists of only one unit which contains the effective amount of the mGLuR5 modulator.

15 The term “granule” encompasses aggregates of particles, e.g. powder particles, to form a multi-particle entity. In pharmaceutical terms, a granule encompasses small particles gathered into a larger, permanent aggregate in which the original particles may still be identified. Granules may be obtained in a granulation process, in which powder particles adhere to each other by different physical mechanisms. Processes such as thermoplastic granulation, aqueous or organic solvent based pot granulation, granulation in a tumbling mixer, granulation in a fluidized bed granulator, granulation by spray drying or dry granulation by compaction are known in the field of pharmaceutical compositions.

25 The term “pellet” encompasses a spherical particle typically created by special granulation technologies. A pellet may be produced by layering active material on a starter particle or by extrusion and spheronisation or by pelletizing in a fluidized bed or by thermal melting, forming, cooling processes. Such processes for producing pellets are known in the field of pharmaceutical formulation development.

30 The term “pharmaceutically acceptable” in connection with a substance encompasses an ingredient or a substance which does not affect the safety of a human being and/or is well-tolerated by a human being after administration. The term “polymorphic form” encompasses an active substance, a pharmaceutically acceptable salt, solvate or isomer thereof forming different crystal structures or lattices.

35

The term “tablet” defines any solid pharmaceutical composition comprising the active substance. The term also encompasses compressed and non-compressed formulations. Non compressed tablets can be manufactured e.g. by thermal or melting processes. <tablets can

be coated or non-coated. The coating can be functional or non-functional be e.g. controlling the release of the drug substance from the tablet.

Tablet may have any shape, which is common in the field of tablets, such as a round shape, a rectangular shape or an oval shape, or a convex shape, or the shape of a disk, or the shape of a bead. The shape may also be irregular. The term tablet also comprises the term “mini-tablet” and “micro-tablet”. Such term is known in the field of pharmaceutical compositions. The mini-tablet has a diameter of less than 6 mm, often from 1 to 5.5 mm.

A mini-tablet can e.g. have a weight from 10 to 50 mg. A tablet may be made from granules and/or pellets. The processing of granules and or pellets into tablets is known to a person skilled in the art.

The invention also relates to pharmaceutical formulations comprising at least one negative allosteric modulator (NAM) of the metabotropic glutamate receptor 5 and at least one excipient for the delayed release for the active substance. These formulations avoid negative effects of the active substances (NAMs) on the gastric system. These formulations can lead to a preferred metabolism scheme of the anti-Parkinson products. The formulations can in particular be used for the treatment of Levodopa-induced dyskinesia (LID). They have e.g. a beneficial effect on the mobility of Parkinson's disease (PD) patients.

Several clinical studies using negative allosteric modulators of the mGluR5 receptor for the treatment of Parkinson's disease have failed in the past due to a lack of efficacy. One issue can be the fluctuating pharmacokinetic effect related to an unpredictable release of the active substance from the stomach. The mechanism that causes the fluctuating release from the stomach and the fluctuation in bioavailability of these compounds is related to the location of mGluR5 in the parasympathetic nerve systems. The gastrointestinal tract has its own nervous system, the enteric nervous system. This is regulated through the autonomic nervous system (ANS). The parasympathetic component of the ANS has a major influence to the digestion e.g. by increasing peristalsis and the secretion of digestive enzymes, regulation of the muscular tone in the stomach and the sphincter relaxation. This parasympathetic effect to the stomach is partly regulated by mGluR5.

As was observed in preclinical experiments, an inhibition of this receptor subtype causes a reduction of the parasympathetic activation. This can lead to a constriction of the sphincter followed by an increase of time for the passage through the stomach, labelled as delay of

gastric emptying. This effect, transmitted via mGluR5, was found to be a local effect and is not induced by systemic treatment (e.g. intravenous treatment) with mGluR5 antagonist. Several pharmaceutical uses of modulators of mGluR5 have been discussed.

- 5 In the publication "Novel treatments of GERD: Focus on the lower esophageal sphincter", A. Lehmann describes (in *Eur Rev Med Pharmacol Sci.* 2008 Aug; 12 Suppl 1:103-110), that certain negative allosteric modulators of mGluR5 can reduce the acid reflux. The compounds MPEP, MTEP and ADX10059 are mentioned in this publication.
- 10 In the publication "New insights in the neural regulation of the lower oesophageal sphincter", L.A. Blackshaw describes (in *Eur Rev Med Pharmacol Sci.* 2008 Aug; 12 Suppl 1:33-39), that gastro-oesophageal reflux disease can be treated with modulators of mGluR5. In the publication "Reflux inhibitors: A new approach for GERD", G.E. Boeckxstaens describes (in *Current Opin Pharmacol.* 2008 Dec; 8(6):685-689), that
- 15 antagonists of mGluR5 can inhibit the reflux of the gastric content into the esophagus. In the publication "Peripheral versus central modulation of gastric vagal pathways by metabotropic glutamate receptor", R. L. Young describes (in *Am J Physiol Gastrointest Liver Physiol.* 2007 Feb; 292(2):G501-511), that the compound 2-methyl-6-phenylethynyl-pyridine (MPEP) has a local influence on the gastric vagal pathway.
- 20 In the publication "Transient lower esophageal sphincter relaxations in dogs are inhibited by a metabotropic glutamate receptor 5 antagonist", J. Jensen describes (in *Eur J Pharmacol.* 2005 Sep 5; 519(1-2):154-157), that MPEP, a specific antagonist of mGluR5 receptors, has an inhibitory effect on transient lower esophageal sphincter relaxation. In the
- 25 publication "Gastrointestinal dysfunction in Parkinson's Disease", W.H. Jost describes in *Neurol Sci.* 2010 Feb 15; 289(1-2):69-73, that Parkinson patients often have a disturbed gastrointestinal motility which often leads to therapeutic problems. In the publication "Autonomic disturbances in Parkinson's disease and their treatment", E. Schneider describes (in *Nervenarzt* 1999 Jan; 70 Suppl 1, S26-34) that in Parkinson patients often
- 30 obstipation can be observed which can lead to a therapeutic problem. In the publication "Autonomic dysfunctions in idiopathic Parkinson's disease", W.H. Jost describes (in *J Neurol.* 2003 Feb; 250 Suppl 1:I28-30), that gastrointestinal trouble is the most common vegetative symptom in parkinsonian syndrome, which can lead to difficulties with oral medication.
- 35 In the publication "Glutamate receptors as therapeutic targets for Parkinson's disease", K.A. Johnson describes (in *CNS Neurol Disord Drug Targets.* 2009 Dec; 8(6):475-491), that dopamine replacement therapies, including levodopa treatment, do not solve the

therapeutic problems for Parkinson patients. For a symptomatic treatment, antagonists of the N-methyl-D-aspartate (NMDA) receptor are proposed. Several negative allosteric modulators of mGluR5 receptors are mentioned to be effective for Parkinson.

- 5 In the publication "Role for metabotropic glutamate receptor 5 (mGluR5) in the pathogenesis of fragile X syndrome", G. Dölen proposes (in J Physiol. 2008 Mar 15; 586(6):1503-8), that antagonists of the mGluR receptor can become important for the treatment of the fragile X syndrome.
- 10 The local effect of negative modulators of the mGluR5 receptor, causing delayed gastric emptying can be avoided according to the present invention by the use of special formulations, such as enteric tablets or capsules, containing active substances which are negative modulators of the mGluR5 receptor. In the literature, several chemical structures for negative modulators of mGluR5 have already been described.
- 15 For example, several types of pyrazolopyrimidine compounds have been disclosed in the literature, see in particular WO 2008/015269 but also WO 2008/015270, WO 2008/015271, WO 2009/095253, WO 2009/095254 and WO2007/006530, which pyrazolopyrimidines are negative modulators of mGluR5. In WO 2004/087153 various
- 20 pyrazolopyrimidines are described, which can act as small molecule immune potentiators (SMIP) and which can be used e.g. for cancer treatment. In WO 2004/089471, the use of substituted pyrazolo[1,5-a]pyrimidines for the treatment of diseases is described where it is desirable to inhibit the enzyme 11 β HSD1. In WO 2003/037900, further specific pyrazolopyrimidine compounds are described as inhibitors of ion-channels in human cells.
- 25 In WO 2003/101993 several types of pyrazolopyrimidine compounds and their use for the treatment of hepatitis infections are disclosed. In the document WO 2003/091256 particular pyrazolopyrimidine derivatives which have a NADPH-oxidase inhibitor activity are described. The compounds described in these documents in particular those of WO 2008/015269, can be used for the formulations of the present invention.
- 30 As further examples for mGluR5 negative allosteric modulators, several types of tetrahydroquinolinone compounds have been disclosed e.g. in WO 2005/082856 and WO 2009/095253. Further negative modulators of mGluR5 are described having a quinolinon structure, other examples are octahydro-indole derivatives, like those described in
- 35 WO2007/006530.

The enteric coating of an active substance can determine the location within the gastrointestinal system where the formulation can be dissolved and the active compound

can be absorbed. Enteric coating prevents the release of the active substance before it reaches the small intestine and is inert or dissolves only slowly at acidic pH but becomes more rapidly dissolving at neutral or alkaline pH level.

- 5 This issue becomes particularly relevant in Parkinson disease (PD) patients. Gastrointestinal symptoms are a common and burdensome non-motor manifestation of PD. They are due to dysfunction of the autonomic nervous systems and lead to the expression of pooling saliva, pharyngeal or oesophageal dysphagia, delayed gastric emptying, constipation and difficulty defecating. Several studies reported that up to 100% of PD
10 patients show some gastric emptying abnormality during the course of the disease.

This invention relates to an enteric formulation to enhance efficacy in particular for the treatment of Levodopa-induced dyskinesia (LID) in PD patients. With the specific formulation, a high benefit of the modulators can be reached in PD patients and can
15 prevent a further delay of gastric emptying. In this context, the pyrazolopyrimidines of WO 2008/015269 are of particular interest. Some of the common gastrointestinal dysfunctions of PD patients can be treated with medications. Pooling saliva e.g. can be treated with atropine-like drugs and constipation with laxatives. However, for some other gastrointestinal symptoms, such as delayed gastric emptying, an adequate treatment is
20 lacking. The delayed gastric emptying can cause a reduced absorption of orally administered anti-PD medication. For example, Levodopa is taken up mainly in the duodenum. The treatment of PD patients with the specific formulations is a new approach for Levodopa-induced dyskinesia (LID). In addition to the dyskinesia-suppressing effect, these formulations have additional beneficial effects on the primary symptoms of PD.

25 Other indication areas are gastroesophageal reflux disease, fragile X syndrome, migraine and some others. This enteric formulation is useful to overcome the problem of delayed gastric emptying and to avoid further side effects regarding to a delay release of e.g. L-Dopa. Based on an enteric formulation, the release of the substance will occur within the
30 small intestine, mainly in the duodenum. Regarding to the fact that the effect on gastric emptying is a local effect, the resorption of the material with the duodenum will no longer effect the stomach and cause no delay of gastric emptying.

The invention provides a formulation, such as a tablet, a capsule, a granule and/or a pellet,
35 comprising as an active substance at least one negative allosteric modulator of the mGluR5 receptor and at least one release-controlling excipient, where the pharmaceutical formulation releases the active substance, namely the at least one negative allosteric modulator of the mGluR5, in the small and/or large intestine.

The pharmaceutical formulation, comprising the negative allosteric modulator of the mGluR5 receptor and at least one layer of enteric coating, are made in a way (by choosing the components of the enteric coating), so that the pharmaceutical formulation releases the negative allosteric modulator of the mGluR5 receptor in the small and/or large intestine and not into the stomach. The enteric formulation preferably does not release substantial amounts of the active substance, namely the negative allosteric modulator of the mGluR5, into the stomach. The amount of the mGluR5 modulators released into the stomach should be less than 10 % by weight (in particular less than 5%) of the active substance, in particular less than 3%, often less than 1% by weight.

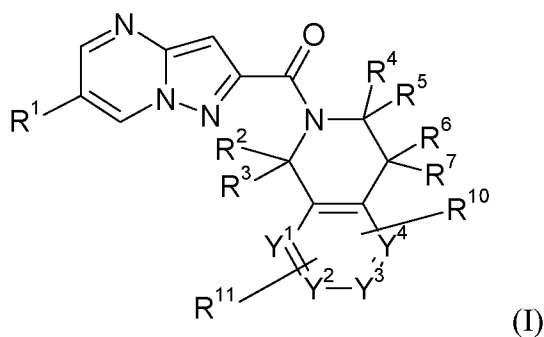
The invention in particular provides a formulation, such as a tablet, a capsule, a granule and/or a pellet, comprising as an active substance at least one negative allosteric modulator of the mGluR5 receptor and at least one release-controlling excipient, in particular at least one layer of enteric coating. The invention relates to a pharmaceutical formulation, comprising at least one negative allosteric modulator of the mGluR5 receptor and at least one pharmaceutically acceptable excipient, where the pharmaceutical formulation is preferably an enteric tablet or an enteric capsule.

The invention relates to a pharmaceutical formulation, comprising 1 to 800 mg, often from 1 to 600 mg of a negative allosteric modulator compound and at least one layer of an enteric polymer coating which is resistant to gastric acids. The weight ratio of enteric polymer coating and modulator compound can be from 500 : 1 to 0.01 : 10, in particular from 50 : 1 to 0.1 : 1. The weight ratio of enteric polymer coating and modulator compound can also be from 500 : 1 to 1 : 10, in particular from 50 : 1 to 3 : 1.

One aspect are pharmaceutical formulations, comprising 1 to 800 mg of a negative allosteric modulator compound and at least one layer of an enteric polymer coating which is resistant to gastric acids, wherein the negative allosteric modulator of the mGluR5 receptor is in the form of a multiple unit dosage form (such as a mini tablet).

The invention also relates to a pharmaceutical formulation, comprising an enteric tablet or enteric capsule, having an enteric polymer coating with a thickness of 5 to 900 micrometer. The invention relates to a pharmaceutical formulation comprising an enteric polymer coating which is resistant to gastric acids for at least 4 hours, preferably for at least 24 hours, but which allows at least 50 % of the negative allosteric modulator compound to be released from the formulation at a pH of 6.8 or higher within 60 minutes.

The invention also relates to a pharmaceutical formulation comprising as negative allosteric modulator of the mGluR5 receptor a compound from the group comprising pyrazolo[1,5-a]pyrimidines, tetrahydroquinolinones, fused pyridines, ethinyl-substituted fused pyridines, ethinyl-substituted tetrahydro-quinolones or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof. Furthermore, the invention relates to a pharmaceutical formulation comprising as negative allosteric modulator of the mGluR5 receptor a pyrazolo[1,5-a]pyrimidine compound of formula (I) or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof,



wherein the radicals denote:

Y¹ represents N or C-,

15 Y² represents N or C-,

Y³ represents N or C-,

Y⁴ represents N or C-,

where at least two of the groups Y¹ to Y⁴ denote a carbon atom,
(often all groups Y¹ to Y⁴ denote a carbon atom),

20 R¹ represents chloro or bromo;

R² and R³ each independently represent hydrogen, C₁-₆alkyl, C₃-₇cycloalkyl or trifluoromethyl; or

R² and R³ both together with the carbon atom of the ring represent a carbonyl group;

25 R⁴ and R⁵ each independently represent hydrogen, C₁-₆alkyl, C₃-₇cycloalkyl or trifluoromethyl; or

R⁴ and R⁵ both together with the carbon atom of the ring represent a carbonyl group;

R⁶ and R⁷ independently represent hydrogen, C₁-₆-alkyl, C₃-₇cycloalkyl or trifluoromethyl; or R⁶ and R⁷ both together with the carbon atom of the ring represent a carbonyl group;

R² or R³ together with R⁶ and R⁷ may also form a bivalent radical from the group

30 CH₂-CH₂ or CH₂-O;

R¹⁰ and R¹¹ independently represent hydrogen, halogen, amino, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, aryl, C₁-₆alkyl, C₃-₇cycloalkyl, C₂-₆alkenyl, C₂-₆alkynyl,

C_{1-6} alkoxy, C_{3-7} -cycloalkyloxy, C_{2-6} alkenyloxy, C_{2-6} alkynyloxy, heteroaryl, heterocyclyl, aryloxy, heteroaryloxy, heterocyclyloxy, C_{1-6} alkylamino, di- C_{1-6} alkylamino, C_{3-7} -cycloalkylamino, di- C_{3-7} -cycloalkylamino, C_{1-6} alkyl- C_{3-7} -cycloalkylamino, C_{2-6} alkenylamino, C_{2-6} alkynylamino, di- C_{2-6} alkenylamino, di- C_{2-6} alkynylamino, C_{1-6} alkyl- C_{2-6} -alkenylamino,

5 C_{1-6} alkyl- C_{2-6} -alkynylamino, C_{2-6} alkenyl- C_{3-7} -cycloalkylamino, C_{2-6} alkynyl- C_{3-7} -cycloalkylamino, C_{2-6} alkenyl- C_{2-6} -alkynylamino arylamino, diarylamino, aryl- C_{1-6} alkylamino, aryl- C_{2-6} alkenylamino, aryl- C_{2-6} alkynylamino, aryl- C_{3-7} -cycloalkylamino, heteroaryl-amino, diheteroaryl-amino, heteroaryl- C_{1-6} alkylamino, heteroaryl- C_{2-6} alkenylamino, heteroaryl- C_{2-6} alkynylamino, heteroaryl- C_{3-7} -cycloalkylamino, heteroarylaryl-amino,

10 heterocyclylamino, diheterocyclylamino, heterocyclyl- C_{1-6} alkylamino, heterocyclyl- C_{2-6} alkenylamino, heterocyclyl- C_{2-6} alkynylamino, heterocyclyl- C_{3-7} -cycloalkylamino, heterocyclylaryl-amino, heterocyclylhetero-aryl-amino, acyl, acyloxy, acylamino, C_{1-6} alkoxycarbonyl, C_{3-7} -cycloalkoxy-carbonyl, C_{2-6} alkenyloxy-carbonyl, C_{2-6} alkynyl-oxycarbonyl, aryloxy-carbonyl, heteroaryloxy-carbonyl, heterocyclyloxy-carbonyl,

15 aminocarbonyl, C_{1-6} alkylamino-carbonyl, di- C_{1-6} alkylaminocarbonyl, C_{3-7} -cycloalkylaminocarbonyl, di- C_{3-7} -cycloalkylaminocarbonyl, C_{1-6} alkyl- C_{3-7} -cycloalkylaminocarbonyl, C_{2-6} alkenyl-aminocarbonyl, C_{2-6} alkynylaminocarbonyl, di- C_{2-6} alkenylaminocarbonyl, di- C_{2-6} alkynylaminocarbonyl, C_{1-6} alkyl- C_{2-6} -alkenylaminocarbonyl, C_{1-6} alkyl- C_{2-6} -alkynylaminocarbonyl, C_{2-6} alkenyl- C_{3-7} -cycloalkylaminocarbonyl, C_{2-6} alkynyl- C_{3-7} -cycloalkylaminocarbonyl,

20 C_{2-6} alkenyl- C_{2-6} -alkynylaminocarbonyl, arylaminocarbonyl, diarylamino-carbonyl, aryl- C_{1-6} alkylaminocarbonyl, aryl- C_{2-6} alkenylaminocarbonyl, aryl- C_{2-6} alkynylaminocarbonyl, aryl- C_{3-7} -cycloalkylaminocarbonyl heteroarylaminocarbonyl, diheteroarylaminocarbonyl, heteroaryl- C_{1-6} alkylaminocarbonyl, heteroaryl- C_{2-6} alkenylaminocarbonyl, heteroaryl- C_{2-6} alkynylaminocarbonyl, heteroaryl- C_{3-7} -cycloalkylaminocarbonyl, heteroarylarylaminocarbonyl, heterocyclylaminocarbonyl,

25 diheterocyclylamino-carbonyl, heterocyclyl- C_{1-6} alkylaminocarbonyl, heterocyclyl- C_{2-6} alkenylamino-carbonyl, heterocyclyl- C_{2-6} alkynylaminocarbonyl, heterocyclyl- C_{3-7} -cycloalkylaminocarbonyl, heterocyclylarylaminocarbonyl, heterocyclylheteroarylaminocarbonyl, C_{1-6} alkylsulfinyl, C_{3-7} -cycloalkylsulfinyl, C_{2-6} alkenylsulfinyl, C_{2-6} alkynylsulfinyl, arylsulfinyl, heteroarylsulfinyl, heterocyclylsulfinyl, C_{1-6} alkylsulfonyl, C_{3-7} -cycloalkylsulfonyl, C_{2-6} alkenylsulfonyl, C_{2-6} alkynylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heterocyclylsulfonyl, C_{1-6} alkylsulfonylamino, or arylsulfonylamino;

or R^{10} and R^{11} together with the two carbon atoms carrying them represent a heteroaryl having 5 or 6 ring members or a heterocyclyl group having 5 or 6 ring members, which

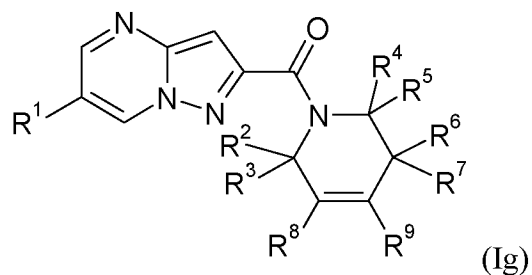
35 can be substituted by one of the following groups: halogen, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, C_{1-6} alkyl and C_{1-6} alkoxy, in particular by methyl. The preferred compounds of this general formula (I) used in the formulation are described more in detail in WO 2008/015269. The particularly useful compounds of formula (I) for the

specific formulations of this invention are specified in the claims of WO 2008/015269, in particular the compounds describes in the experimental part of this application. To the definitions of the radicals made in this document WO 2008/015269 reference is made explicitly.

5

The invention also relates to a pharmaceutical formulation, comprising as negative allosteric modulator of the mGluR5 receptor a pyrazolo[1,5-a]pyrimidine compound of formula (Ig) or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof,

10



wherein

R¹ represents chloro or bromo;

R², R³, R⁴, R⁵, R⁶ and R⁷, which may be the same or different, each independently represent hydrogen, C₁-₆alkyl, amino, hydroxy, halogen, or trifluoromethyl;

15

R⁸ and R⁹ together with the carbon atoms to which they are attached may form an unsaturated cyclic ring system containing 5 to 7 (i.e. 5, 6 or 7) carbon atoms, wherein 0 to 4 (i.e. 0, 1, 2, 3 or 4) of the carbon atoms of the ring system formed by R⁸ and R⁹ may be replaced by heteroatoms independently selected from nitrogen, oxygen and sulfur and

20

wherein the ring system may be optionally substituted by one or more (e.g., 1, 2, or 3) substituents, which may be the same or different, independently selected from halogen, amino, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, aminocarbonyl, N-C₁-₆alkylaminocarbonyl, di-N,N-C₁-₆alkylaminocarbonyl, C₁-₆alkyl, hydroxyC₁-₆alkyl, C₂-₆alkenyl, C₁-₆alkoxy, C₁-₆alkoxycarbonyl, C₁-₆alkylcarbonyloxy, C₁-₆alkylamino, di-C₁-₆alkylamino, C₁-₆alkylcarbonylamino, C₁-₆alkylenedioxy, aryl, heteroaryl, heterocyclyl, and cycloC₃-₁₂alkyl.

25

The preferred compounds of this general formula (Ig) used in the formulation are described more in detail in WO 2008/015269. The particularly useful compounds of formula (Ig) are specified in the claims of WO 2008/015269 and in the experimental part.

30

The invention relates to a pharmaceutical formulation comprising as negative allosteric modulator of the mGluR5 receptor a pyrazolo[1,5-a]pyrimidine compound of formula (Ig)

or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof, wherein the radicals denote:

R¹ represents chloro or bromo;

5 R², R³, R⁴, R⁵, R⁶ and R⁷, which may be the same or different, each independently represent hydrogen, C₁₋₆alkyl, amino, hydroxy, halogen, or trifluoromethyl;

R⁸ and R⁹ together with the carbon atoms to which they are attached may form an unsaturated cyclic ring system containing 5 to 7 carbon atoms, wherein 0 to 4 of the carbon atoms of the ring system formed by R⁸ and R⁹ may be replaced by heteroatoms
10 independently selected from nitrogen, oxygen and sulfur and wherein

the ring system may be optionally substituted by one or more substituents, which may be the same or different, independently selected from halogen, amino, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, aminocarbonyl, N-C₁₋₆alkylaminocarbonyl, di-N,N-C₁₋₆alkylaminocarbonyl, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, C₁₋₆alkoxycarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkylamino, di-C₁₋₆alkylamino, C₁₋₆alkylcarbonylamino, C₁₋₆alkylenedioxy, aryl, heteroaryl, heterocyclyl, and cycloC₃₋₁₂alkyl.
15

In a preferred embodiment of the invention, compounds are used wherein R⁸ and R⁹ together with the carbon atoms to which they are attached, form a phenyl ring system.

20

The invention relates to a pharmaceutical formulation comprising as negative allosteric modulator of the mGluR5 receptor a pyrazolo[1,5-a]pyrimidine or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph of the following compounds:

25

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

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

30 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

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

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3,3-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
35

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

- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dimethoxy-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 5 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dimethoxy-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 10 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-hydroxy-7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-hydroxy-7-methoxy-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 15 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dimethoxy-3-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dimethoxy-3-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dimethoxy-3,3-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 20 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dimethoxy-3,3-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-5,8-dihydro-6H-[1,7]naphthyridin-7-yl)-methanone
- 25 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-5,8-dihydro-6H-[1,7]naphthyridin-7-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-[2,7]naphthyridin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-[2,7]naphthyridin-2-yl)-methanone
- 30 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-[2,6]naphthyridin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-[2,6]naphthyridin-2-yl)-methanone
- 35 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-methyl-7,8-dihydro-5H-[1,6]naphthyridin-6-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-methyl-7,8-dihydro-5H-[1,6]naphthyridin-6-yl)-methanone

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

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

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

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

10 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-fluoro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone;

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

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

15 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-fluoro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

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

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

20 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-fluoro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

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

25 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-fluoro-1-ethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

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

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

30 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-fluoro-1-ethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

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

35 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-fluoro-1-ethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

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

- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-fluoro-1-ethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-fluoro-1-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 5 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-fluoro-1-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-fluoro-1-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 10 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-fluoro-1-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-fluoro-1-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-fluoro-1-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 15 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-fluoro-1-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-fluoro-1-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-ethyl-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 20 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-((R)-3-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-((S)-3-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 25 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (7-Bromo-3,4-dihydro-1H-isoquinolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
- (7-Bromo-3,4-dihydro-1H-isoquinolin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
- 30 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-fluoro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,4-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 35 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,4-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,4-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,4-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,4-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 5 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,4-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-methoxy-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-methoxy-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 10 (6-Bromopyrazolo[1,5-a]pyrimidin-2yl)-(1-ethyl-3,4-dihydro-1H-isoquinolin-2-yl)methanone
- (6-Bromopyrazolo[1,5-a]pyrimidin-2yl)-(1-isopropyl-3,4-dihydro-1H-isoquinolin-2-yl)methanone
- 15 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-isopropyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-ethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 20 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (7-Bromo-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
- 25 (7-Bromo-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-cyclohexyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-cyclohexyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 30 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-propyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-((S)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone;
- 35 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-((R)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone;
- (5-Bromo-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-5-methoxy-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (5-Bromo-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
- 5 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-pyridin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-methoxy-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 10 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-methoxy-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5,6-dimethoxy-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 15 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5,8-difluoro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(5,8-difluoro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-5-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 20 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-5-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-methyl-7,8-dihydro-5H-[1,6]naphthyridin-6-yl)-methanone
- 25 (3-Bromo-7,8-dihydro-5H-[1,6]naphthyridin-6-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyridin-3-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (3-Bromo-7,8-dihydro-5H-[1,6]naphthyridin-6-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
- 30 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-pyridin-3-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-isoquinoline-7-carbonitrile
- 35 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-pyridin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-nitro-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

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

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

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

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

10 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-morpholin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

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

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

15 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-morpholin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

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

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

20 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyrimidin-5-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

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

25 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-5-pyrimidin-3-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

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

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

30 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

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

35 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,7-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

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

- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,5-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (7-Chloro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
- 5 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-chloro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (5-Chloro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
- 10 N-[2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-acetamide
- N-[2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-acetamide
- N-[2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-isoquinolin-5-yl]-acetamide
- 15 N-[2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-isoquinolin-5-yl]-acetamide
- N-[2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-isoquinolin-5-yl]-acetamide
- 20 2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-isoquinoline-5-carboxylic acid dimethylamide
- 2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-isoquinoline-5-carboxylic acid dimethylamide
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-2,3,5,8-tetrahydro-6H-1,4-dioxo-7-aza-phenanthren-7-yl)-methanone
- 25 2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-isoquinoline-5-carbonitrile
- 2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-isoquinoline-7-carbonitrile
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyridin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 30 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyridin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyridin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 35 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyridin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-methyl-8,9-dihydro-6H-[1,3]dioxolo[4,5-f]isoquinolin-7-yl)-methanone

- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-5-pyridin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-5-pyridin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 5 (6-Bromo-3,4-dihydro-1H-isoquinolin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyridin-2-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyridin-2-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 10 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyridin-2-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-pyridin-2-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 15 (5-Bromo-3,4-dihydro-1H-isoquinolin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
- (5-Bromo-3,4-dihydro-1H-isoquinolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-pyridin-2-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 20 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[5-(2,4-dimethoxy-pyrimidin-5-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[5-(2,4-dimethoxy-pyrimidin-5-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 25 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[5-(2,6-dimethoxy-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[5-(2,6-dimethoxy-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[5-(6-fluoro-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 30 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[5-(6-fluoro-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[5-(2-methoxy-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 35 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[5-(2-methoxy-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[5-(6-methoxy-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone

- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[5-(6-methoxy-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[6-(2-methoxy-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 5 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[6-(2-methoxy-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[6-(2-fluoro-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[6-(2-fluoro-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 10 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[6-(6-fluoro-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[6-(6-fluoro-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 15 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[6-(2,6-dimethoxy-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[6-(2,6-dimethoxy-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[6-(2,4-dimethoxy-pyrimidin-5-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 20 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[6-(2,4-dimethoxy-pyrimidin-5-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[7-(6-methoxy-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 25 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[7-(2-methoxy-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[7-(2,4-dimethoxy-pyrimidin-5-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[7-(2,4-dimethoxy-pyrimidin-5-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 30 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[7-(2-fluoro-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[7-(2-fluoro-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 35 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[5-(2-fluoro-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[5-(2-fluoro-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone

- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-furan-2-yl-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-furan-2-yl-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 5 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-furan-2-yl-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-furan-2-yl-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-8-(5-methyl-furan-2-yl)-3,4-
- 10 dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-7-(5-methyl-furan-2-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-6-(5-methyl-furan-2-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 15 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-5-(5-methyl-furan-2-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-furan-3-yl-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-furan-3-yl-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 20 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-furan-3-yl-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-furan-3-yl-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 25 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[8-(3,5-dimethyl-isoxazol-4-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[7-(3,5-dimethyl-isoxazol-4-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[6-(3,5-dimethyl-isoxazol-4-yl)-1-
- 30 methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[5-(3,5-dimethyl-isoxazol-4-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-8-(1H-pyrazol-4-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 35 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-7-(1H-pyrazol-4-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-6-(1H-pyrazol-4-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone

- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-5-(1H-pyrazol-4-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-8-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 5 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 10 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-5-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-8-(3-methyl-1H-pyrazol-4-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-7-(3-methyl-1H-pyrazol-4-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 15 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-6-(3-methyl-1H-pyrazol-4-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-5-(3-methyl-1H-pyrazol-4-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 20 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-8-(2H-tetrazol-5-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-7-(2H-tetrazol-5-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-6-(2H-tetrazol-5-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 25 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-5-(2H-tetrazol-5-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-[2,7]naphthyridin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-[2,6]naphthyridin-2-yl)-methanone
- 30 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-methyl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-5,8-dihydro-6H-pyrido[3,4-d]pyrimidin-7-yl)-methanone
- 35 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-5-nitro-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-nitro-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-nitro-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-8-nitro-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 5 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-5-nitro-3,4-dihydro-1H-[2,7]naphthyridin-2-yl)-methanone
- 2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-isoquinoline-5-carbonitrile
- 2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-isoquinoline-5-carboxylic acid methyl ester
- 10 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(2,6-dimethyl-8,9-dihydro-6H-3-oxa-1,7-diaza-cyclopenta[a]naphthalen-7-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(4-methyl-1,4-dihydro-2H-[3,7]phenanthrolin-3-yl)-methanone
- 15 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(2,6-dimethyl-8,9-dihydro-6H-thiazolo[4,5-f]isoquinolin-7-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-methanesulfonyl-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-methanesulfonyl-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 20 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-methanesulfonyl-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methanesulfonyl-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 25 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(4,7-dimethyl-1,4,7,8,9,10-hexahydro-2H-[3,7]phenanthrolin-3-yl)-methanone
- 1-[2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-isoquinolin-5-yl]-ethanone
- 2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-isoquinoline-6-carboxylic acid methyl ester
- 30 2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-isoquinoline-7-carboxylic acid methyl ester
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-5-(morpholine-4-carbonyl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 35 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-7-(morpholine-4-carbonyl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-6-(morpholine-4-carbonyl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone

- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-methyl-8,9-dihydro-6H-furo[3,2-f]isoquinolin-7-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3,6-dimethyl-3,6,8,9-tetrahydro-pyrrolo[3,2-f]isoquinolin-7-yl)-methanone
- 5 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-5,8-dihydro-6H-furo[3,2-g]isoquinolin-7-yl)-methanone
- 7-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-2,6-dimethyl-1,2,6,7,8,9-hexahydro-pyrrolo[3,4-f]isoquinolin-3-one
- 7-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-2,6-dimethyl-2,3,6,7,8,9-hexahydro-pyrrolo[3,4-f]isoquinolin-1-one
- 10 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-diethylamino-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-diethylamino-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 15 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-diethylamino-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-diethylamino-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-difluoro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 20 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-difluoro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dichloro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 25 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dichloro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dibromo-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dibromo-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 30 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-morpholin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-morpholin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 35 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-8-morpholin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-8-morpholin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

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

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

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

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

10 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-piperidin-1-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

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

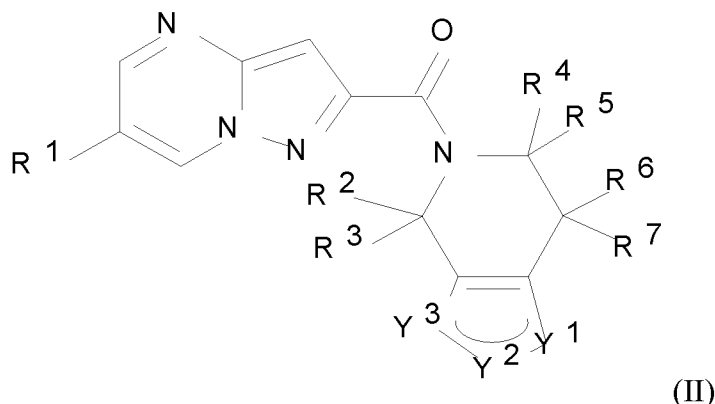
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-pyrrolidin-1-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

15 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-pyrrolidin-1-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone.

20 The two enantiomers (R and S) of the compound (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone are of particular interest for the specific enteric formulations, in particular the R-isomer.

25 The invention also relates to a pharmaceutical formulation, comprising the compound (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-R-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone and at least one layer of enteric coating, where the enteric coating comprises one or several of the following copolymers: methyl acrylate/methacrylic acid copolymers, methyl methacrylate/methacrylic acid copolymers and methacrylic acid/ethyl acrylate copolymers. These formulations are of particular use for the treatment of CNS-disorders, in particular of Parkinson disease. Of particular interest are enteric coated mini-tablets, comprising 5 to 40 mg of the particular pyrazolopyrimidin and at least one layer of enteric coating.

35 The invention also relates to a pharmaceutical formulation, comprising as negative allosteric modulator of the mGluR5 receptor a pyrazolo[1,5-a]pyrimidine compound of formula (II) or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof,



wherein

Y^1 , Y^2 and Y^3 independantly are CR^{10} , CR^{11} , $CR^{10}R^{11}$, NR^{12} , S or O,

5 whereby at least one of Y^1 , Y^2 and Y^3 denotes CR^{10} ;

or Y^1 and Y^2 together denote a group $R^{10}C=N$; $R^{10}C=CR^{11}$; $R^{10}R^{11}C-C(=O)$ or $R^{12}N-C(=O)$;

or Y^2 and Y^3 together denote a group $R^{10}C=N$; $R^{10}C=CR^{11}$; $R^{10}R^{11}C-C(=O)$ or $R^{12}N-C(=O)$;

10 R^1 represents chloro or bromo;

R^2 represents hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl or trifluoromethyl;

R^3 represents hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl or trifluoromethyl; or

R^2 and R^3 together with the carbon atom of the ring represent a carbonyl group

R^4 represents hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl or trifluoromethyl;

15 R^5 represents hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl or trifluoromethyl; or

R^4 and R^5 together with the carbon atom of the ring represent a carbonyl group;

R^6 represents hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl or trifluoromethyl;

R^7 represents hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl or trifluoromethyl;

R^6 and R^7 together with the carbon atom of the ring represent a carbonyl group;

20 R^2 or R^3 together with R^6 or R^7 may form a bivalent radical of type CH_2-CH_2 or CH_2-O ;

R^{10} , R^{11} independantly represent hydrogen, halogen, amino, hydroxy, nitro, cyano,

trifluoromethyl, trifluoromethoxy, aryl, C_{1-6} alkyl, C_{3-7} -cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl,

C_{1-6} alkoxy, C_{3-7} -cycloalkyloxy, C_{2-6} alkenyloxy, C_{2-6} alkynyloxy, heteroaryl, heterocyclyl,

aryloxy, heteroaryloxy, heterocyclyloxy, C_{1-6} alkylamino, di- C_{1-6} alkylamino, C_{3-7} -

25 cycloalkylamino, di- C_{3-7} -cycloalkylamino, C_{1-6} alkyl- C_{3-7} -cycloalkylamino, C_{2-6}

alkenylamino, C_{2-6} alkynylamino, di- C_{2-6} alkenylamino, di- C_{2-6} alkynylamino, C_{1-6} alkyl- C_{2-6}

alkenylamino, C_{1-6} alkyl- C_{2-6} alkynylamino, C_{2-6} alkenyl- C_{3-7} -cycloalkylamino, C_{2-6}

alkynyl- C_{3-7} -cycloalkylamino, C_{2-6} alkenyl- C_{2-6} alkynylamino arylamino, diarylamino,

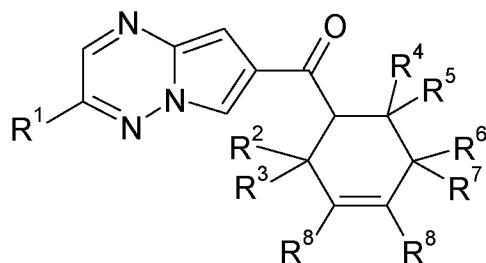
aryl- C_{1-6} alkylamino, aryl- C_{2-6} alkenylamino, aryl- C_{2-6} alkynylamino, aryl- C_{3-7} -

30 cycloalkylamino, heteroarylamino, diheteroarylamino, heteroaryl- C_{1-6} alkylamino,

heteroaryl-C₂₋₆alkenylamino, heteroaryl-C₂₋₆alkynylamino, heteroaryl-C₃₋₇-
 cycloalkylamino, heteroarylaryl-amino, heterocyclylamino, diheterocyclylamino,
 heterocyclyl-C₁₋₆alkylamino, heterocyclyl-C₂₋₆alkenylamino, heterocyclyl-C₂₋₆
 alkynylamino, heterocyclyl-C₃₋₇-cycloalkylamino, heterocyclylaryl-amino,
 5 heterocyclylhetero-aryl-amino, acyl, acyloxy, acylamino, C₁₋₆alkoxycarbonyl, C₃₋₇-
 cycloalkoxy-carbonyl, C₂₋₆alkenylloxycarbonyl, C₂₋₆alkynylloxycarbonyl, aryloxycarbonyl,
 heteroaryloxycarbonyl, heterocyclylloxycarbonyl, aminocarbonyl, C₁₋₆alkylamino-
 carbonyl, di-C₁₋₆alkylaminocarbonyl, C₃₋₇-cycloalkylaminocarbonyl, di-C₃₋₇-
 cycloalkylaminocarbonyl, C₁₋₆alkyl-C₃₋₇-cycloalkylaminocarbonyl, C₂₋₆alkenyl-
 10 aminocarbonyl, C₂₋₆alkynylaminocarbonyl, di-C₂₋₆alkenylaminocarbonyl, di-C₂₋₆-
 alkynylaminocarbonyl, C₁₋₆alkyl-C₂₋₆-alkenylaminocarbonyl, C₁₋₆alkyl-C₂₋₆-alkynyl-
 aminocarbonyl, C₂₋₆alkenyl-C₃₋₇-cycloalkylaminocarbonyl, C₂₋₆alkynyl-C₃₋₇-
 cycloalkylaminocarbonyl, C₂₋₆alkenyl-C₂₋₆-alkynylaminocarbonyl, arylaminocarbonyl,
 diarylaminocarbonyl, aryl-C₁₋₆alkylaminocarbonyl, aryl-C₂₋₆alkenylaminocarbonyl, aryl-
 15 C₂₋₆alkynylaminocarbonyl, aryl-C₃₋₇-cycloalkylaminocarbonyl heteroarylaminocarbonyl,
 diheteroarylaminocarbonyl, heteroaryl-C₁₋₆alkylaminocarbonyl, heteroaryl-C₂₋₆alkenyl-
 aminocarbonyl, heteroaryl-C₂₋₆alkynylaminocarbonyl, heteroaryl-C₃₋₇-cycloalkyl-
 aminocarbonyl, heteroarylarylaminocarbonyl, heterocyclylaminocarbonyl, dihetero-
 cyclylamino-carbonyl, heterocyclyl-C₁₋₆alkylaminocarbonyl, heterocyclyl-C₂₋₆alke-
 20 nylamino-carbonyl, heterocyclyl-C₂₋₆alkynylaminocarbonyl, heterocyclyl-C₃₋₇-cycloalkyl-
 aminocarbonyl, heterocyclylarylaminocarbonyl, heterocyclylheteroaryl-amino-carbonyl, C₁₋₆-
 alkylsulfinyl, C₃₋₇-cycloalkylsulfinyl, C₂₋₆alkenylsulfinyl, C₂₋₆alkynylsulfinyl,
 arylsulfinyl, heteroarylsulfinyl, heterocyclylsulfinyl, C₁₋₆alkylsulfonyl, C₃₋₇-
 cycloalkylsulfonyl, C₂₋₆alkenylsulfonyl, C₂₋₆alkynylsulfonyl, arylsulfonyl,
 25 heteroarylsulfonyl, heterocyclylsulfonyl, C₁₋₆alkylsulfonylamino or arylsulfonylamino;
 and R¹² represents hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, acyl, aryl,
 heteroaryl, heterocyclyl, C₁₋₆alkylamino-carbonyl, di-C₁₋₆alkylamino-carbonyl, C₁₋₆-
 alkylsulfonyl, arylsulfonyl or heteroarylsulfonyl.

30 The preferred compounds of this general formula (II) used in the formulation are described
 more in detail in WO 2008/015270. The particularly useful compounds of formula (II) are
 specified in the claims of WO 2008/015270. To the definitions of the radicals made in this
 document reference is made explicitly.

35 The invention relates to a pharmaceutical formulation comprising as negative allosteric
 modulator of the mGluR5 receptor a pyrazolo[1,5-a]pyrimidine compound of formula (III)
 or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph
 thereof,

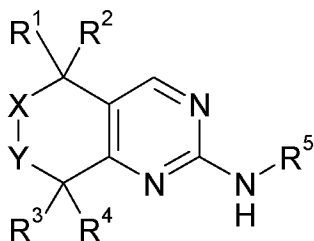


(III)

wherein

- 10 R¹ represents chloro or bromo;
 R² and R³ each independently represent hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl or trifluoromethyl; or
 R² and R³ both together with the carbon atom of the ring represent a carbonyl group;
 R⁴ and R⁵ each independently represent hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl or
 15 trifluoromethyl; or
 R⁴ and R⁵ both together with the carbon atom of the ring represent a carbonyl group;
 R⁶ and R⁷ independently represent hydrogen, C₁₋₆-alkyl, C₃₋₇cycloalkyl or trifluoromethyl;
 or R⁶ and R⁷ both together with the carbon atom of the ring represent a carbonyl group;
 R² or R³ together with R⁶ and R⁷ may also form a bivalent radical from the group
 20 CH₂-CH₂ or CH₂-O;
 R⁸ represents a radical R⁹ or a radical R¹⁰, whereby one of the two radicals R⁸ denotes R⁹
 and the other radical R⁸ denotes R¹⁰;
 R⁹ represents a cyclic group selected from aryl, heteroaryl or heterocyclyl, wherein the ring
 system may be optionally substituted by one or two substituents, which may be the same or
 25 different and selected independently from halogen, amino, hydroxyl, nitro, cyano,
 trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl, hydroxyC₁₋₆alkyl and C₁₋₆alkoxy;
 R¹⁰ represents hydrogen or C₁₋₆alkyl. The preferred compounds of this general formula
 (III) used in the formulation are described more in detail in WO 2008/015271. The
 particularly useful compounds of formula (III) are specified in the claims of WO
 30 2008/015271. To the definitions of the radicals made in this document reference is made
 explicitly.

The invention relates to a pharmaceutical formulation, comprising as negative allosteric
 modulator of the mGluR5 receptor an amino-substituted fused pyrimidine compound of
 35 formula (IV) or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or
 polymorph thereof,



(IV)

wherein

X represents CH_2 , $\text{CR}^6(\text{C}=\text{O})\text{R}^7$, or NR^8 ;

Y represents CR^9R^{10} or NR^{11} ;

R^1 represents H, C_{1-6} alkyl, or F;

R^2 represents H, C_{1-6} alkyl, or F;

or R^1 and R^2 together with the carbon atom to which they are attached form a carbonyl group;

or R^1 and R^2 together with the carbon atom to which they are attached form a 3-7 membered ring which may be saturated or unsaturated, wherein the ring may optionally contain one or two heteroatoms selected from sulfur, oxygen, and nitrogen and wherein the ring may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, hydroxy, cyano, acyl, C_{1-6} alkylamino, di- $(\text{C}_{1-6}$ alkyl)amino, C_{1-6} alkylcarbonylamino, and oxo;

R^3 represents H, C_{1-6} alkyl, or F;

R^4 represents H, C_{1-6} alkyl, or F;

or R^3 and R^4 together with the carbon atom to which they are attached form a 3-7 membered ring which may be saturated or unsaturated, wherein the ring may optionally contain one or two heteroatoms selected from sulfur, oxygen, and nitrogen and wherein the ring may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C_{1-6} alkyl, C_{1-6} alkoxy, amino, hydroxy, cyano, acyl, C_{1-6} alkylamino, di- $(\text{C}_{1-6}$ alkyl)amino, C_{1-6} alkylcarbonylamino, and oxo;

R^5 represents a monocyclic moiety selected from aryl, heteroaryl, cyclo C_{3-6} alkyl, and heterocyclyl;

R^6 represents H, C_{1-6} alkyl which may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C_{1-6} alkoxy, amino, hydroxy, C_{1-6} alkylamino, and di- $(\text{C}_{1-6}$ alkyl)amino, or F;

R^7 represents C_{1-6} alkyl, which may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C_{1-6} alkoxy, amino, hydroxy, C_{1-6} alkylamino, and di- $(\text{C}_{1-6}$ alkyl)amino, cyclo C_{3-6} alkyl, heterocyclyl, or $\text{NR}^{12}\text{R}^{13}$;

or R^6 and R^7 together with the carbon atoms to which they are attached form a 3-7 membered ring which may be saturated or unsaturated, wherein the ring may optionally

contain one or two heteroatoms selected from sulfur, oxygen, and nitrogen and wherein the ring may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl, C₁₋₆alkoxy, amino, hydroxy, cyano, acyl, C₁₋₆alkylamino, di-(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonylamino, and oxo;

- 5 R⁸ represents C₁₋₆alkyl which may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, C₃₋₆cycloalkyl, heterocyclyl, aryl, heteroaryl, C₁₋₆alkylcarbonyl which may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, C₃₋₆cycloalkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, C₁₋₆alkoxycarbonyl which may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, aminocarbonyl, N-C₁₋₆alkylaminocarbonyl, wherein the alkyl moiety may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, N,N-di-(C₁₋₆alkyl)aminocarbonyl, wherein the alkyl moieties may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, C₁₋₆alkylsulfonyl, wherein the alkyl moiety may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, C₃₋₆cycloalkylsulfonyl, aminosulfonyl, N-C₁₋₆alkylaminosulfonyl, wherein the alkyl moiety may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, or N,N-di-(C₁₋₆alkyl)aminosulfonyl, wherein the alkyl moieties may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino;

R⁹ represents H, C₁₋₆alkyl, or F; R¹⁰ represents H, C₁₋₆alkyl, or F;

- 30 or R⁹ and R¹⁰ together with the carbon atom to which they are attached form a 3-7 membered ring which may be saturated or unsaturated, wherein the ring may optionally contain one or two heteroatoms selected from sulfur, oxygen, and nitrogen and wherein the ring may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl, C₁₋₆alkoxy, amino, hydroxy, cyano, acyl, C₁₋₆alkylamino, di-(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonylamino, and oxo;

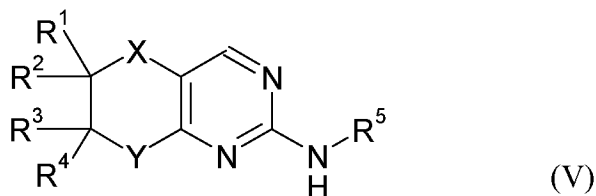
35 R¹¹ represents C₁₋₆alkyl which may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, C₃₋₆cycloalkyl, heterocyclyl, aryl, heteroaryl, C₁₋

alkylcarbonyl which may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, C₃₋₆cycloalkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, C₁₋₆alkoxycarbonyl, which may be optionally substituted by one or
5 more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, aminocarbonyl, N-C₁₋₆alkylaminocarbonyl, wherein the alkyl moiety may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, N,N-di-(C₁₋₆alkyl)aminocarbonyl, wherein the alkyl moieties may be optionally substituted by one or
10 more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, C₁₋₆alkylsulfonyl, wherein the alkyl moiety may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, C₃₋₆cycloalkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aminosulfonyl, N-C₁₋₆alkylaminosulfonyl, wherein the alkyl moiety may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, or N,N-di-(C₁₋₆alkyl)aminosulfonyl, wherein the alkyl moieties may be optionally substituted
15 by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino;
R¹² represents H, C₁₋₆alkyl, or C₃₋₆cycloalkyl;
R¹³ represents H, C₁₋₆alkyl, or C₃₋₆cycloalkyl;
or R¹² and R¹³ together with the carbon atom to which they are attached form a 3-7
25 membered ring which may be saturated or unsaturated, wherein the ring may optionally contain one or two heteroatoms selected from sulfur, oxygen, and nitrogen and wherein the ring may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl, C₁₋₆alkoxy, amino, hydroxy, cyano, acyl, C₁₋₆alkylamino, di-(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonylamino, and oxo.

30 The preferred compounds of this general formula (IV) used in the formulation are described more in detail in EP 10 196 570.5, filed 22.12.2010 (see PCT/EP2011/073712) and in the patent claims of this document. To the definitions of the radicals made in this document reference is made explicitly.

35 The invention relates to a pharmaceutical formulation comprising as negative allosteric modulator of the mGluR5 receptor an amino-substituted fused pyrimidine compound of

formula (V) or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof,



wherein

X represents CH₂ or C=O;

10 Y represents CR⁶R⁷, NR⁸, O or S;

R¹ represents H, C₁₋₆alkyl, or F;

R² represents H, C₁₋₆alkyl, or F;

or R¹ and R² together with the carbon atom to which they are attached form a 3-7 membered ring which may be saturated or unsaturated, wherein the ring may optionally contain one or two heteroatoms selected from sulfur, oxygen, and nitrogen and wherein the ring may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl, C₁₋₆alkoxy, amino, hydroxy, cyano, acyl, C₁₋₆alkylamino, di-(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonylamino, and oxo;

R³ represents H, C₁₋₆alkyl, or F; R⁴ represents H, C₁₋₆alkyl, or F;

or R³ and R⁴ together with the carbon atom to which they are attached form a 3-7 membered ring which may be saturated or unsaturated, wherein the ring may optionally contain one or two heteroatoms selected from sulfur, oxygen, and nitrogen and wherein the ring may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl, C₁₋₆alkoxy, amino, hydroxy, cyano, acyl, C₁₋₆alkylamino, di-(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonylamino, and oxo;

R⁵ represents a monocyclic moiety selected from aryl, heteroaryl, cycloC₃₋₆alkyl, and heterocyclyl;

R⁶ represents H, C₁₋₆alkyl, or F; R⁷ represents H, C₁₋₆alkyl, or F;

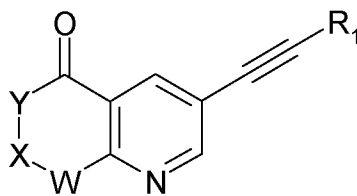
or R⁶ and R⁷ together with the carbon atom to which they are attached form a 3-7 membered ring which may be saturated or unsaturated, wherein the ring may optionally contain one or two heteroatoms selected from sulfur, oxygen, and nitrogen and wherein the ring may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl, C₁₋₆alkoxy, amino, hydroxy, cyano, acyl, C₁₋₆alkylamino, di-(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonylamino, and oxo;

R⁸ represents H, C₁₋₆alkyl which may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, C₃₋₆cycloalkyl, C₁₋₆alkylcarbonyl which may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl,

trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, C₃₋₆cycloalkylcarbonyl, C₁₋₆alkoxycarbonyl which may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, aminocarbonyl, N-C₁₋₆alkylaminocarbonyl wherein the alkyl moiety may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, N,N-di-(C₁₋₆alkyl)aminocarbonyl, wherein the alkyl moieties may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino.

The preferred compounds of this general formula (V) used in the formulation are described more in detail in EP 10 196 573.9, filed 22.12.2010 (see PCT/EP2011/073711) and in the patent claims of this document. To the definitions of the radicals made in this document reference is made explicitly.

The invention relates to a pharmaceutical formulation comprising as negative allosteric modulator of the mGluR5 receptor an ethynyl-substituted fused pyridine compound of formula (VI) or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof,



(VI)

wherein

R₁ represents aryl, heteroaryl, cycloC₃₋₁₂alkyl, cycloC₅₋₁₂alkenyl, or heterocyclyl;

W represents CH₂, -CR₂R₃CH₂-, O, S, or NR₄;

X represents CR₂R₃ or NR₅;

Y represents CH₂, -CH₂CH₂-, or NR₆;

R₂ represents hydrogen, fluorine, hydroxy, C₁₋₆alkyl, aryl-C₁₋₆alkyl, or heteroaryl-C₁₋₆alkyl;

R₃ represents hydrogen or C₁₋₆alkyl; or R₂ and R₃ together with the carbon atom to which they are attached form a 3-7 membered ring which may be saturated or unsaturated, wherein the ring may optionally contain one or two heteroatoms selected from sulfur, oxygen, and nitrogen and wherein the ring may be optionally substituted by one or more substituents selected from halogen, fluoromethyl, difluoromethyl, trifluoromethyl,

trifluoromethoxy, C₁₋₆alkyl, C₁₋₆alkoxy, amino, hydroxy, cyano, acyl, C₁₋₆alkylamino, di-(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonylamino, and oxo;

R₄ represents hydrogen, C₁₋₆alkyl, or acyl; R₅ represents hydrogen, C₁₋₆alkyl, or acyl; and R₆ represents hydrogen, C₁₋₆alkyl, or acyl;

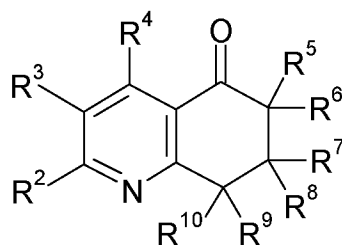
- 5 wherein the term "aryl" means phenyl or naphthyl, wherein the phenyl or naphthyl group is optionally substituted by one or more substituents, which may be the same or different, selected independently from halogen, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkyl, amino, hydroxy, nitro, cyano, formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkoxycarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkylcarbonyloxyC₁₋₆alkyl, C₁₋₆alkylamino, di-(C₁₋₆alkyl)amino, cycloC₃₋₁₂alkylamino, C₁₋₆alkylcarbonylamino, phenylcarbonylamino, aminocarbonyl, N-C₁₋₆alkylaminocarbonyl, di-N,N-C₁₋₆alkylaminocarbonyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, cycloC₃₋₁₂alkyl, pyridinyl, and C₁₋₆alkylenedioxy;
- 10
- 15 the term "heteroaryl" means an aromatic 5-6 membered ring containing from one to four heteroatoms selected from oxygen, sulfur and nitrogen, or a bicyclic group comprising a 5-6 membered ring containing from one to four heteroatoms selected from oxygen, sulfur and nitrogen fused with a benzene ring or a 5-6 membered ring containing from one to four heteroatoms selected from oxygen, sulfur and nitrogen, wherein the heteroaryl group may
- 20 be optionally substituted by one or more substituents, which may be the same or different, selected independently from halogen, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, amino, hydroxy, nitro, cyano, C₁₋₆alkylcarbonyl, C₁₋₆alkoxycarbonyl, C₁₋₆alkoxycarbonyloxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, cycloC₃₋₁₂alkylamino, C₁₋₆alkylcarbonylamino, aminocarbonyl, N-C₁₋₆alkylaminocarbonyl, di-N,N-C₁₋₆alkylaminocarbonyl, pyrrolidinyl, piperidinyl, morpholinyl, cycloC₃₋₁₂alkyl, C₁₋₆alkylenedioxy, aryl, and pyridinyl.
- 25

The preferred compounds of this general formula (VI) used in the formulation are described more in detail in EP 10 187 954.2, filed 18.10.2010 (see PCT/EP2011/068205), and in the patent claims of this document. To the definitions of the radicals made in this document reference is made explicitly.

30

The invention relates to a pharmaceutical formulation comprising as negative allosteric modulator of the mGluR5 receptor a tetrahydroquinolinone compound of formula (VII) or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof,

35



(VII)

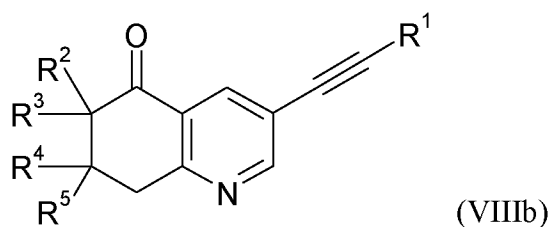
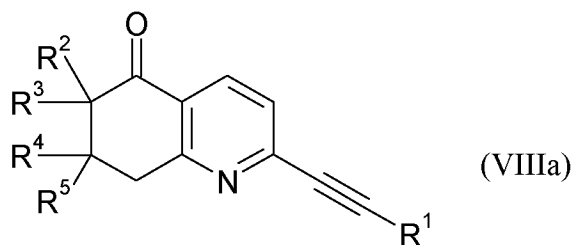
wherein R₂ represents C₂₆alkyl, cycloC₃12alkyl, cycloC₃12alkyl-C₁₆alkyl, C₂₆alkenyl, C₂₆alkynyl, aryl, biaryl, aryl-heteroaryl, heteroaryl- heteroaryl, heteroaryl-aryl, aryl-Ci-
 eatkyf, aryl-C₂₆alkenyl, aryl- C₂-6alkynyl, heteroaryl, heteroaryl-C₁-6alkyl, heteroaryl-
 C₂-6alkenyl, heteroaryl-C₂-6alkynyl, 2, 3-dihydro-1 H-indenyl, C₂-6alkoxy, hydroxy-
 C₂₆alkoxy, cycloC₃-12alkoxy, cycloC₃-12alkyl-C₁-6alkoxy, aryloxy, aryl- C₁-6alkoxy,
 C₁-6alkoxy-C₁-6alkyl, C₁-6alkylthio, C₄-6alkenylthio, cycloC₃-12alkylthio, cycloC₃-
 12alkyl-C₁-6alkylthio, cycloC₃-12alkyl- C₃6alkenylthio, C₁-6alkoxy-C₁-6alkylthio, C₁-
 6alkoxy-C₃-6alkenylthio, aryl-C₃6alkenylthio, heteroaryl-C₁6alkylthio, C₁6alkylsulfonyl,
 cycloC₃-12alkyl-C₁-6alkylsulfonyl, arylC₁-6alkylsulfonyl, C₁-6alkylamino, di-C₁-
 6alkylamino, cycloC₃-12alkylamino, C₁-6alkoxy- cycloC₃-12alkylamino, cycloC₃-
 12alkyl-C₁-6alkylamino, di-C₁-6 alkylamino-C₁₆alkyl, C₁-6alkoxy-C₂-6alkylamino,
 arylamino, aryl- IC₁-6alkylamino, N-cycloC₃-12alkyl-N-C₁-6alkylamino, N-aryl-N- C₁-
 6alkylamino, N-arylC₁-6alkyl-N-C₁-6alkylamino, 2-indanylamino, 1,2, 3, 4-
 tetrahydroisoquinolin-2-yl, tetrahydrofuryl, pyrrolidino, piperidino, 4-arylpiperidino, 4-
 heteroarylpiperidino, morpholino, piperazino, 4-C₁-6alkylpiperazino, 4-arylpiperazino,
 hexamethyleneimino, benzazepinyl, 1, 3-dihydro-2H-isoindol-2-yl, heteroaryl-C₁6alkoxy,
 heteroarylamino, heteroaryl-C₁-6alkylamino, - NHC (=O)-R", -NHSO₂-R", -NHC(=O)OR"
 , -C (=O) NH-R", or -C₁-6alkyl-C(=O)NH-R₁₁, wherein the cycloC₃-12alkyl is optionally
 unsaturated and wherein one carbon atom in the cycloC₃-12alkyl moiety may be replaced
 by an oxygen atom or an NR₁₂-moiety ; R₃ represents hydrogen, cyano, nitro, halogen, 1-
 6alkyl, CF₃, heteroaryl, 2, 3-dihydro-1H-indenyl, hydroxy, C₁-6alkoxy, pyrrolidino,
 piperidino, or morpholin ; R₄ represents hydrogen, halogen, nitro, C₁-6alkoxy, or
 hydroxy-C₂₆ alkoxy ; R₅ and R₆, which may be the same or different, each independently
 represent hydrogen, hydroxy, C₁-6alkyl, cycloC₃-12alkyl, C₂-6alkenyl, C₁-6alkoxy, C₁-
 6alkoxy-C₁-6alkyl, C₁-6alkylthio, C₃-6alkenylthio, C₁-6 alkylamino, di-C₁-6alkylamino,
 cycloC₃-12alkylamino, di-C₁-6 alkylamino- C₁₆alkyl, aryl-C₁-6alkylamino, aryl, aryl-C₁-
 6alkyl, or aryl-C₂₆alkenyl ; or one of R₅ and R₆ and one of R₇ and R₈ together represent -
 (CH₂)_n- with n being 3,4 or 5, while the remaining of R₅ and R₆ as well as R₇ and R₈ are
 both hydrogen; R₇ and R₈, which may be the same or different, each independently
 represent hydrogen, C₁-6alkyl, cycloC₃-12alkyl, C₂-6alkenyl, cycloC₃-12 alkyl-C₁-
 6alkyl, aryl, aryl-C₁-6alkyl, heteroaryl, or heteroaryl-C₁₆alkyl ; or R₇ and R_a may

together represent- (CH₂)_m- with m being 4,5 or 6; R₉ and R₁₀, which may be the same or different, each independently represent hydrogen, dealkyl, hydroxy, or dealkoxy; R₁₁ represents hydrogen, C1-6alkyl, C2-6alkenyl, aryl, aryl-C1-6alkyl, aryl-C2-6alkenyl, heteroaryl, heteroaryl-C1-6alkyl, C1-6alkylamino, di-C1-6alkylamino, cycloC3-12alkylamino, di-C1-6alkylamino-C1-6alkyl, arylamino, aryl-C1-6alkylamino, aryl-C2-6alkenylamino, N-aryl-N-C1-6alkylamino, pyrrolidino, piperidino, morpholino, hexamethyleneimino, benzazepinyl, 1, 3-dihydro-2H-isoindol-2-yl, cycloC₃₋₁₂alkyl, or cycloC₃₋₁₂alkyl-C1-6alkyl, wherein the cycloC₃₋₁₂alkyl is optionally unsaturated and wherein one carbon atom in the cycloC₃₋₁₂alkyl moiety may be replaced by an oxygen atom or an NR₁₂-moiety;

R₁₂ represents hydrogen, C1-6alkyl, aryl, heteroaryl, aryl-C1-6alkyl or heteroaryl-C1-6alkyl.

The preferred compounds of this general formula (VII) used in the formulation are described more in detail in WO 2005/082856 and in the patent claims of this document. To the definitions of the radicals made in this document reference is made explicitly.

The invention relates to a pharmaceutical formulation comprising as negative allosteric modulator of the mGluR5 receptor an ethynyl-substituted tetrahydro-quinolinone compound of formula (VIIIa) or (VIIIb) or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof,



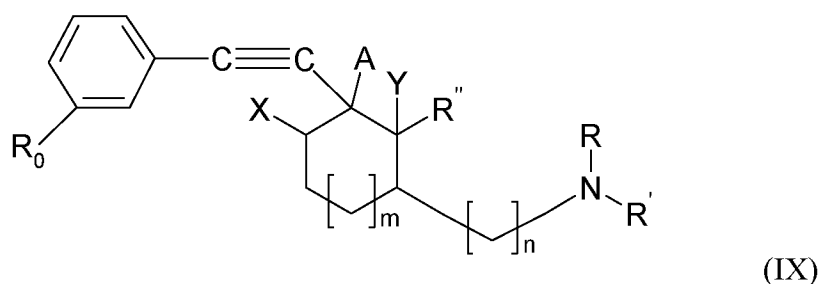
wherein

R^1 represents aryl or heteroaryl, which may be optionally substituted by one substituent selected from amino, C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkylamino, and di- $(C_{1-6}$ alkyl)amino; R^2 represents hydrogen or C_{1-6} alkyl; R^3 represents hydrogen or C_{1-6} alkyl; R^4 represents hydrogen or C_{1-6} alkyl; R^5 represents hydrogen or C_{1-6} alkyl.

The preferred compounds of this general formula (VIIIa) used in the formulation are described more in detail in WO 2007/023242, filed 24.8.2005, and WO 2007/023290 (see also EP-A 1 931 635) and in the patent claims of these documents. To the definitions of the radicals made in this document reference is made explicitly.

The preferred compounds of this general formula (VIIIb) used in the formulation are described more in detail in EP 10 187 954.2, filed 18.10.2010 (see PCT/EP2011/068205) and in the patent claims of this document. To the definitions of the radicals made in this document reference is made explicitly.

The invention relates to a pharmaceutical formulation comprising as negative allosteric modulator of the mGluR5 receptor a phenyl-ethynyl-substituted heterocyclic compound of formula (IX) or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof,



wherein m is 0 or 1, n is 0 or 1 and

A is hydroxy

X is hydrogen and

Y is hydrogen, or

A forms a single bond with X or with Y ;

R_0 is hydrogen, $(C_{1-4}$ alkyl), $(C_{1-4}$ alkoxy, trifluoromethyl, halogen, cyano, nitro, - $COOR_1$ wherein R_1 is $(C_{1-4}$ alkyl or - COR_2 wherein R_2 is hydrogen or $(C_{1-4}$ alkyl, and

R is - COR_3 , - $COOR_3$, - $CONR_4R_5$ or - SO_2R_6 , wherein R_3 is $(C_{1-4}$ alkyl, $(C_3$ -

$7)$ cycloalkyl or optionally substituted phenyl, 2-pyridyl or 2-thienyl, R_4 and R_5 ,

independently, are hydrogen or $(C_{1-4}$ alkyl and R_6 is $(C_{1-4}$ alkyl, $(C_3$ -7)cycloalkyl or

optionally substituted phenyl,

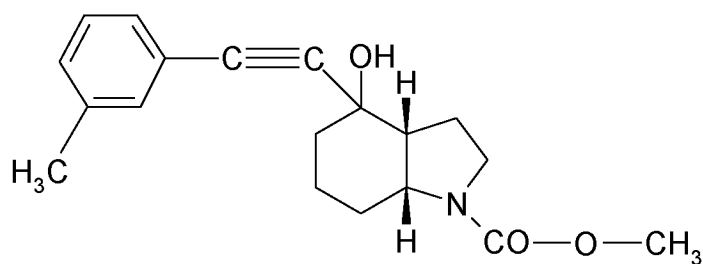
R' is hydrogen or (C₁₋₄alkyl and

R" is hydrogen or (C₁₋₄alkyl, or

R' and R" together form a group -CH₂-(CH₂)_m- wherein m is 0, 1 or 2, in which
 5 case one of n and m is different from 0, with the proviso that R₀ is different from
 hydrogen, trifluoromethyl and methoxy when n is 0, A is hydroxy, X and Y are
 both hydrogen, R is COOEt and R' and R" together form a group -(CH₂)₂-.

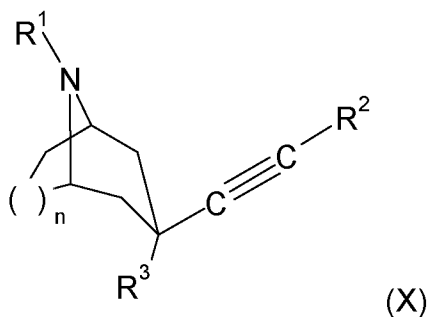
The preferred compounds of this general formula (IX) used in the formulation are
 10 described more in detail in WO 2007/006530 and in the patent claims of this document.
 To the definitions of the radicals made in this document reference is made explicitly.

The compound of formula (IXa), namely (3aR,4S,7aR)-methyl-4-hydroxy-4-(m-tolyl-
 ethynyl)octahydro-1H-indole-1-carboxylate, can be used in the specific formulations.



(IXa)

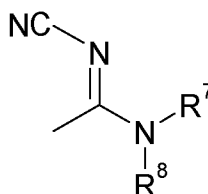
The invention relates to a pharmaceutical formulation comprising as negative allosteric
 20 modulator of the mGluR5 receptor an ethynyl-substituted bi-cyclic compound of formula
 (X) or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph
 thereof,



(X)

wherein n represents 1 or 2;

R¹ represents C₁₋₆alkyl which may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, C₃₋₆cycloalkyl, heterocyclyl, aryl, heteroaryl, C₁₋₆alkylsulfonyl which may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, C₃₋₆cycloalkylsulfonyl, -C(O)R⁴, or



R² represents aryl, heteroaryl, cycloC₃₋₁₂alkyl, or heterocyclyl;

R³ represents H, F, OH, C₁₋₆alkoxy;

R⁴ represents C₁₋₆alkyl which may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, C₃₋₆cycloalkyl, heterocyclyl, C₁₋₆alkoxy which may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, or -NR⁵R⁶;

R⁵ and R⁶ which may be the same or different represent H or C₁₋₆alkyl which may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, or

R⁵ and R⁶ together with the nitrogen atom to which they are attached form a 3-7 membered ring which may be saturated or unsaturated, wherein the ring may optionally contain one or two additional heteroatoms selected from sulfur, oxygen, and nitrogen and wherein the ring may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, di-(C₁₋₆alkyl)amino, and oxo;

R⁷ and R⁸ which may be the same or different represent H or C₁₋₆alkyl which may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, or

R⁷ and R⁸ together with the nitrogen atom to which they are attached form a 3-7 membered ring which may be saturated or unsaturated, wherein the ring may optionally contain one or two additional heteroatoms selected from sulfur, oxygen, and nitrogen and wherein the ring may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, di-(C₁₋₆alkyl)amino, and oxo.

The preferred compounds of this general formula (X) used in the formulation are described more in detail in EP 11 165 897.7 (filed May 12, 2011) and in the patent claims of this document. To the definitions of the radicals made in this document reference is made explicitly. Many of the compounds have a azabicyclo[3.2.1]octane system.

A further aspect of the invention is a process for the preparation of a pharmaceutical formulation as described above, comprising the step of preparing e.g. a tablet or a capsule containing at least one negative allosteric modulator of the mGluR5 receptor and then providing the tablet or capsule with at least one layer of an enteric coating.

The invention relates to the use of a formulation as described above for the treatment or prevention of a condition or disease from the following:

Alzheimer's disease, Parkinson's disease, Parkinson's dementia, mild cognitive impairment, L-dopa-induced dyskinesias (LID), L-dopa-induced dyskinesias in Parkinson's disease, dyskinesias, drug induced dyskinesias, dopaminomimetic-induced dyskinesias, tremor, anxiety disorders, social anxiety disorder (SAD), dementia, dementia in Alzheimer's disease, major depressive disorder, depression, migraine, movement disorders, pain, chronic pain, neuropathic pain and gastroesophageal reflux disease (GERD).

The invention relates to the use of a formulation for the treatment or prevention of Parkinson's disease, Parkinson's dementia, L-dopa-induced dyskinesias (LID), L-dopa-induced dyskinesias in Parkinson's disease, dyskinesias, drug induced dyskinesias, dopaminomimetic-induced dyskinesias, tremor, anxiety disorders, depression, migraine, chronic pain, neuropathic pain and gastroesophageal reflux disease (GERD).

Other indication areas according to the invention are synucleinopathies, alpha-synucleinopathies, Lewy body dementia, Neurodegeneration with Brain Iron Accumulation, Multiple

system atrophy, Parkinson-plus syndrome, Pick's disease progressive supranuclear palsy (PSP), frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17).

5 The invention relates to a pharmaceutical formulation comprising at least two different active substances, which contains at least one a negative allosteric modulator of the mGluR5 receptor and at least one active substance from the group:

Levo-Dopa, Carbidopa, Benserazid, L-Serine-2-(2,3,4-trihydroxy-benzyl)-hydrazide, L-Tyrosine-2-(2,3,4-trihydroxy-benzyl)-hydrazide and Glycine-2-(2,3,
10 4-trihydroxy-benzyl)-hydrazide.

The invention relates to a pharmaceutical formulation comprising a substituted pyrazolo[1,5-a]pyrimidine compound (in particular a compound of formula (I) or (Ig)) as
15 negative allosteric modulator of the mGluR5 receptor and Levo-Dopa or the compound Carbidopa.

A typical tablet, capsule, granule or pellet has a diameter (longest diameter) of from 0.1 to 18 mm, often from 1 to 10 mm, where the measurement of the diameter may be performed by microscopical methods or by a caliper gauge. In one embodiment of the invention, each
20 tablet, capsule, granule or pellet has a weight ranging from 1 to 1500 mg.

The invention also relates to a pharmaceutical formulation comprising the negative allosteric modulator of the mGluR5 receptor in the form of a multiple unit dosage form.

25 Delayed release formulations or dosage forms are known from other active substances, which can be applied e.g. in form of mini-tablets. Mini-tablets comprising a release-controlling excipient are e. g. known from the drug orfiril®, an agent for the treatment of primary (idiopathic) epilepsy. Mini-tablets, small granules and small pellets (in particular enteric coated) have already been described in the literature.

30 Various release dosage forms are available either as single unit (monolithic formulation) or as multiple unit (multi particulate) dosage forms. The single unit dosage forms usually refer to diffusion-controlled systems where the drug is dissolved or dispersed throughout a solid matrix and the release of the drug is controlled or sustained either by incorporating a
35 suitable filler within the matrix or by coating the matrix with swellable or nonswellable polymer film(s). The former case is known as a monolithic system where the diffusion of a drug through a matrix is the rate-limiting step. In monolithic preparations made of polymers the drug release is commonly governed by the swelling rate of the polymer

matrix. In the second case, the diffusion of the drug through the polymer coating or layer of the system is the rate controlling step.

Multiple unit dosage forms, such as mini-tablets, are a preferred embodiment of the invention when drug-excipient or drug-drug interactions may occur in a single unit formulation. They are also found to have less variance in transit time through the gastrointestinal tract than single unit dosage forms. The multiple unit dosage forms usually are based on subunits such as granules, pellets, or mini-tablets. They can be delivered in hard gelatin capsules or transformed into tablets that disintegrate immediately in aqueous media of the gastro-intestinal tract, releasing the delayed release units.

The multiple unit dosage forms, such as mini-tablets, small granules and small pellets (in particular when enteric coated), offer some advantages over the single unit formulation. Multiple unit forms may offer more predictable gastric emptying, gastric emptying less dependent on the state of nutrition, a high degree of dispersion in the digestive tract, less variability of absorption, and a lower risk of dose dumping. However, their manufacturing is sometimes more complicated, the filling of gelatin capsules is difficult to accomplish especially in the case where different subunits are involved, and the preparation process of mini-tablets necessitates extra care and fine adjustments of tableting machines. A typical mini-tablet has a diameter of from 0.1 to less than 6 mm.

In one embodiment of the invention, a multiple unit dosage forms of a modulator of the mGluR5 receptor is provided, wherein the unit is in the form of a tablet, granule, or pellet; or a combination of two or more thereof. In one embodiment, the diameter of the unit is from 0.1 to 5 mm, or is from 0.2 to 4.5 mm, or is from 0.5 to 2.5 mm. In another embodiment, the weight of the unit (e.g. mini-tablet) is from 0.1 to 100 mg, or from 0.1 to 50 mg, or from 1 to 25 mg, or from 2 to 10 mg.

In the formulations of the modulator of the mGluR5 receptor, the enteric polymer coating of the tablets and capsules (or granules or pellets) often is in general from 5 to 900 μm , often also from 10 to 600 μm , or from 20 to 100 μm . The coating thickness can be determined microscopically, e.g. via cross-sectioning a tablet. Such methods are known to a person skilled in the pharmaceutical sciences.

As release-controlling and modifying excipient for the enteric coating, water-swellaable and/or water-insoluble and/or porous polymers are particularly useful. Suitable polymers are generally known to the person skilled in the art. Examples include:

Cellulose polymers and their derivatives including, but not limited to, methylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxybutylcellulose, hydroxyethyl methylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, carboxymethyl ethylcellulose, cellulose acetate phthalate, cellulose acetate succinate , polysaccharides and their derivatives, polyalkylene oxides, polyoxyethylenoxide polymers polyethylene glycols, chitosan, alginate, carrageen, galactomannan, tragacanth, agar, acacia, gellan, guar gum, gum arabicum, gum tragacanth, locust bean gum, xanthan gum, pectin, shellack, carboxymethyl amylopectin, chitosan, maleic anhydride copolymers, polyacrylate, polymethacrylate, methacrylate copolymer, polyvinyl alcohol, polyvinylpyrrolidone, polyvinylpyrrolidone-polyvinyl acetate copolymer, polyvinyl acetate succinate and blends of polyvinylpyrrolidone and polyvinyl acetate, poly(2-ethyl-2-oxazoline), poly(ethyleneimine), polyurethane hydrogels, crosslinked polyacrylic acids and their derivatives, and mixtures of any of these.

From these release-controlling and modifying excipients for the enteric coating, water-swallowable and/or water-insoluble and/or porous polymers are preferred which are resistant to gastric fluid, e. g. at pH 1 to 3, often at pH 1 to 5.5.

In one embodiment of the invention, said release-controlling coating is selected such that in application not more than 10 % by weight of said active substance (modulator of the mGluR5 receptor) are released from said tablet within a period of 2 hours. In a further embodiment, said delayed release formulation is a multiple unit dosage form (such as a mini-tablet). In another aspect, the invention provides a tablet comprising at least two units, preferably at least 10 units, wherein said unit(s) are granules and/or pellets and/or mini-tablets.

According to another aspect, the invention provides a capsule or stickpack, comprising at least one unit or the delayed release dosage form or a tablet comprising at least two units, wherein said unit is a granule and/or a pellet.

In another embodiment, a first release-controlling excipient is a polymer selected from:

polyacrylate, polymethacrylate and/or ethylcellulose;

and at least one second release-controlling excipient is a polymer selected from:

methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxybutylcellulose, hydroxyethyl methylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, carboxymethyl ethylcellulose, polysaccharides and their derivatives, cellulose acetate phthalate, polyalkylene oxides, polyoxyethylenoxide polymers, polyethylene glycols, chitosan, alginate, carrageen, galactomannan, tragacanth, agar, acacia, gellan, guar gum, gum arabicum, gum tragacanth, locust bean gum, xanthan gum, pectin, shellack, carboxymethyl amylopectin, chitosan, maleic anhydride copolymers, polyvinyl alcohol, polyvinylpyrrolidone, polyvinylpyrrolidone-polyvinyl acetate copolymer and blends of polyvinylpyrrolidone and polyvinyl acetate, poly(2-ethyl-2-oxazoline), poly(ethyleneimine), polyurethane hydrogels, crosslinked polyacrylic acids and their derivatives; copolymers of the aforementioned polymers including block copolymers and graft polymers; lipids and waxes including, for example, beeswax, natural or synthetic mono-, di- and triglycerides of medium and long chain fatty acids such as hydrogenated vegetable oils, carnauba wax, petroleum wax, microcrystalline wax, long chain fatty acids, long chain fatty alcohols, esters of fatty acids and fatty alcohols; and mixtures of any of these compounds.

In one embodiment, said at least one first release-controlling excipient is a polymer selected from polyacrylate and/or polymethacrylate. In one embodiment, said poly(meth)acrylate is a non-ionic poly(meth)acrylate. In one embodiment, said non-ionic poly(meth)acrylate is an ester of poly(meth)acrylate.

In one embodiment, said second release-controlling excipient is hydroxypropylmethylcellulose. In another embodiment, said at least one first release-controlling agent is ethylcellulose. In another embodiment, said at least one first release-controlling agent is ethylcellulose; and said at least one second release-controlling excipient is a polyvinyl alcohol or a polyvinyl acetate or a polyvinyl alcohol grafted with polyethylene glycol.

Further suitable components and polymers for the enteric formulations are release-controlling and modifying lipids and waxes including, for example, beeswax, natural or synthetic mono-, di- and triglycerides of medium and long chain fatty acids such as hydrogenated vegetable oils, carnauba wax, petroleum wax, microcrystalline wax, long chain fatty acids, long chain fatty alcohols, esters of fatty acids and fatty alcohols. Further examples are copolymers of the polymers listed above, including block copolymers and graft polymers. Specific examples of copolymers are commercially available polyethylene oxide-polypropylene oxide block copolymers such as known under the trademark Pluronic® and Tectonic® (BASF). Further examples are commercially available

hydrolyzed starch polyacrylonitrile graft polymers, commonly known as "Super Slurper" (Illinois Corn Growers Association). Several release-controlling excipients based on polyvinylpyrrolidone are commercially available e.g. under the trademark Kollidon (BASF), e.g. Kollidon SR. Kollidon SR comprises a physical mixture of polyvinyl acetate and polyvinylpyrrolidone. Specifically, Kollidon SR comprises a mixture of 80 % polyvinyl acetate and 19 % polyvinylpyrrolidone. The mixture contains about 0.8 % sodium lauryl sulfate and 0.2 % silica (by weight).

Some release-controlling excipients based on polymethacrylate and/or polymethacrylate-copolymers are e.g. commercially available under the trademark Eudragit. Grades are e.g. Eudragit RS 30 D, Eudragit RL 30 D, Eudragit NE 40 D, Eudragit RS PO and Eudragit NE 30 D, or a combination of two or more thereof.

Eudragit RS 30 D contains from 6.11 to 8.26 % ammonia methacrylate moieties based on dry substance determined according to Ph. Eur. 2.2.20. Eudragit RL 30 contains from 10.18 to 13.73 % ammonia methacrylate moieties based on dry substance determined according to Ph. Eur. 2.2.20. Eudragit RS PO contains from 4.48 to 6.77 % ammonia methacrylate moieties based on dry substance determined according to Ph. Eur. 2.2.20. Eudragit NE 30 D is a neutral copolymer of ethyl acrylate with methyl methacrylate.

Furthermore, the copolymers of methacrylic acid and ethyl acrylate, such as Eudragit L 100-55, are of particular interest for the coating of pyrazolopyrimidine containing cores.

Among the above-mentioned water-swellaable polymers, some may be considered non-ionic polymers, such as non-ionic cellulose ether. An example of such polymers is hydroxypropyl methylcellulose (HPMC), also called hypromellose, which may be used alone or in combination with other polymers. Different grades of hydroxypropyl methylcellulose according to the invention include commercially available grades such as HPMC 2208, HPMC 2906 and HPMC 2910. These grades differ in their degree of substitution both with regard to the methyl (or methoxyl) and hydroxypropyl (or hydroxypropoxyl) groups. A typical grade of hydroxypropyl methylcellulose is HPMC 2208, which is e.g. commercially available as Methocel K 100M CR. Hydroxypropylcellulose is e.g. commercially available under the trademark Klucel.

Ethylcellulose is e.g. commercially available under the trademark Surelease®. Exemplarily mentioned types are Surelease® E-7-19010 and E-7-19050. Another grade is Surelease® E-7-7050. Surelease® E-7-7050 is an ethylcellulose which contains a plasticizer.

The following polymers can be used to develop a enteric pharmaceutical capsule or tablet (and in particular mini-tablets):

- A) Eudragit L and Eudragit S
- 5 B) CAP – Cellulose acetate phthalate
- C) CAS – Cellulose acetate succinate
- D) HPMCP – Hydroxypropylmethyl cellulose phthalate
- E) HPMCAS - Hydroxypropylmethyl cellulose acetate succinate
- F) PVAP – Polyvinyl acetate phthalate
- 10 G) Shellac.

The products Eudragit L and Eudragit S are of particular interest, they are easily available.

15 The relative amount of enteric coating needed in the formulation to achieve the desired release characteristics depends, inter alia, on the selected polymer type and grade, the presence or absence of other excipients having impact on release of active substance, and on the desired drug load.

20 The ratio of this enteric polymer to the active substance is typically selected in the range from about 500 : 1 to about 1 : 100, or from about 50 : 1 to about 1 : 50, or from about 5 : 1 to about 1 : 10. In one embodiment, the ratio of enteric polymer to active substance is from 50 : 1 to about 3 : 1 (weight/weight). In one embodiment, said delayed release excipients comprise talc or are employed in combination with talc.

25 Depending on the route of administration, e. g. oral, sublingual, rectal, cutaneous, percutaneous or parenteral, an active substance can act systemically or locally. In the case of a systemic action, the active substance reaches the target organ in the bloodstream after absorption. In the case of local action, the point of administration and the point of action are the same (e. g. the stomach), no transport of the active substance is needed.

30

The formulation of the negative allosteric modulator of the mGluR5 receptor is preferably administered orally, often as film coated tablet or sugar coated tablet (dragee). This mode of administration is suitable, as the active compound, in particular the substituted pyrazolopyrimidine of formula (I), is not destroyed by the digestive juices produced by the pancreas. Furthermore, as the modulators of the mGluR5 receptor can have a negative side
35 effect on the stomach, the formulations are advantageous. The modulator of the mGluR5 receptor is better absorbed after having passed through the stomach.

The negative allosteric modulators of the mGluR5 receptor can be formulated as enteric products. These formulations may be therapeutically beneficial in the treatment of conditions which involve abnormal glutamate neurotransmission or in which modulation of mGluR5 receptors results in therapeutic benefit. These formulations are preferably administered in the form of an oral pharmaceutical composition, wherein the drug substance (or a combination of more than one drug substance) is present together with one or more pharmaceutically acceptable excipients.

It is an object of the present invention to provide novel pharmaceutical formulations which comprise at least one negative mGluR5 modulator, in particular the substituted pyrazolopyrimidine of formula (I), and at least one pharmaceutically acceptable excipient for an enteric coating of the active substance. It is a further object of the invention to provide a novel method of treating, eliminating, alleviating, palliating, or ameliorating the above mentioned undesirable CNS disorders which involve abnormal glutamate neurotransmission by employing an enteric coating-formulation of the invention, in particular comprising a substituted pyrazolopyrimidine of formula (I).

Moreover the invention deals with a pharmaceutical formulation comprising the negative allosteric modulator of the mGluR5 receptor (or optical isomers, pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof), in particular the substituted pyrazolopyrimidine of formula (I) (see WO 2008/015269), and one or more pharmaceutically acceptable excipients, at least one DOPA-Decarboxylase-Inhibitor, such as a compound from the group:

Levo-Dopa,
Carbidopa,
Benserazid,

L-Serine-2-(2, 3, 4-trihydroxy-benzyl)-hydrazide
L-Tyrosine-2-(2, 3, 4-trihydroxy-benzyl)-hydrazide
Glycine-2-(2, 3, 4-trihydroxy-benzyl)-hydrazide.

Moreover, the invention relates to a method for treating or preventing a condition or disease associated with abnormal glutamate neurotransmission as described above, such method comprising the step of administering to a living animal, including a human, an enteric formulation of a therapeutically effective amount of a compound selected of those of formula (I) described in WO 2008/015269.

In particular, the invention relates to the use of an enteric formulation of a compound of formula (I) or of formula (Ia) as defined in WO 2008/015269 or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof for the treatment of Alzheimer's disease, Parkinson's disease, Parkinson's dementia, L-dopa-induced dyskinesias (LID), L-dopa-induced dyskinesias in Parkinson's disease, dyskinesias, tremor, anxiety disorders, depression, migraine, chronic pain, neuropathic pain, gastroesophageal reflux disease (GERD) and fragile X syndrome in mammals, including humans.

The invention in particular relates to the use of a enteric formulation, in particular comprising the substituted pyrazolopyrimidine of formula (I), wherein the condition associated with abnormal glutamate neurotransmission is selected from: L-dopa-induced dyskinesias, Parkinson's disease and anxiety disorders.

The invention in particular relates to a pharmaceutical formulation comprising as active ingredient at least one pyrazolopyrimidine-compound of formula (I) as defined in WO 2008/015269 or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof, together with one or more other substances exhibiting neurological effects on Parkinson via a different mechanism.

The combination of l-DOPA with the negative mGluR5-modulator, in particular the substituted pyrazolopyrimidine of formula (I), can be realized in a single enteric pharmaceutical formulation (as principally described in the prior art) comprising the mGluR5 modulator and l-DOPA, in one pharmaceutical formulation.

It is also possible to have two separate pharmaceutical formulations, one comprising an enteric negative mGluR5 modulator and one comprising l-DOPA in a pharmaceutical formulation, to be administered conjointly (simultaneously or sequentially). For the sequential administration to be considered "conjoint", however, the negative mGluR5 modulator of the present invention and the l-DOPA must be administered separated by a time interval that still permits the resultant beneficial effect in a mammal. For example, the mGluR5 modulator and the l-DOPA can be administered on the same day (e.g., each - once or twice daily), preferably within an hour of each other, and most preferably simultaneously. These combination products can e.g. be used for the treatment of Parkinson, dopamin-induced dyskinesias and dopaminomimetic-induced dyskinesias.

The negative allosteric modulators of the mGluR5 receptor of the present invention may be in the form of pharmaceutically acceptable salts. "Pharmaceutically acceptable salts" refers

to those salts which possess the biological effectiveness and properties of the parent compound and which are not biologically or otherwise undesirable.

For the pharmaceutical application, the negative allosteric modulators of the mGluR5
5 receptor, together with one or more excipients are placed into the form of pharmaceutical
formulations (and unit dosages thereof), and in such form are employed as coated tablets or
coated, filled capsules, all for oral use. Such pharmaceutical formulations may comprise
conventional or new ingredients, with or without additional active substances, and such
formulations may contain any suitable effective amount of the active ingredient
10 commensurate with the intended daily dosage range to be employed. Tablets containing 1
to 800 milligrams of active substance or, more broadly, from 0,5 to 1000 milligrams per
coated tablet or capsule are suitable representative forms.

Due to their high degree of activity and their low toxicity, together presenting a most
15 favorable therapeutic index, the negative allosteric modulators of the mGluR5 receptor
may be administered to a subject, e.g., a living animal (including a human) body, in need
thereof, for the treatment, alleviation, or amelioration, palliation, or elimination of an
indication or condition which is susceptible thereto, or representatively of an indication or
condition set forth elsewhere in this application, preferably concurrently, simultaneously,
20 or together with one or more pharmaceutically-acceptable excipients, especially in the
form of a pharmaceutical formulation for the oral route.

Suitable dosage ranges, in particular of the substituted pyrazolopyrimidine of formula (I),
are from 1 to 2400 milligrams daily, preferably 10 to 1500 milligrams daily, depending as
25 usual upon the exact formulation, the medical indication toward which the administration
is directed, the subject involved and the body weight of the subject involved, and the
preference and experience of the physician or veterinarian in charge.

For the oral administration in the form of coated tablet or capsule, the active substance of
30 the formulation may be combined with a non-toxic, pharmaceutically acceptable excipients
such as binding agents (e.g., pregelatinized maize starch, polyvinylpyrrolidone or
hydroxypropyl methylcellulose); fillers (e.g., lactose, sucrose, glucose, mannitol, sorbitol
and other reducing and non-reducing sugars, microcrystalline cellulose, calcium sulfate, or
calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc, or silica, steric
35 acid, sodium stearyl fumarate, glyceryl behenate, calcium stearate, and the like);
disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g.,
sodium lauryl sulphate), coloring and flavoring agents, gelatin, sweeteners, natural and

synthetic gums (such as acacia, tragacanth or alginates), buffer salts, carboxymethylcellulose, polyethyleneglycol, waxes, and the like.

The tablets containing the negative allosteric modulators of the mGluR5 receptor can be coated by methods well known in the art. As disclosed herein, the dose of the components in the formulations of the present invention is determined to ensure that the dose administered continuously or intermittently will not exceed an amount determined after consideration of the results in test animals and the individual conditions of a patient. A specific dose naturally varies depending on the dosage procedure, the conditions of a patient or a subject animal such as age, body weight, sex, sensitivity, feed, dosage period, drugs used in combination, seriousness of the disease.

The appropriate dose and dosage times under certain conditions can be determined by the test based on the above-described indices but may be refined and ultimately decided according to the judgment of the practitioner and each patient's circumstances (age, general condition, severity of symptoms, sex, etc.) according to standard clinical techniques. The potential toxicity and therapeutic efficacy of the formulations of the invention can be determined by standard pharmaceutical procedures in experimental animals, e.g., by determining the NOAEL (No Observed Adverse Effect Level) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between therapeutic and toxic effects is the therapeutic index and it may be expressed as the ratio NOAEL/LD₅₀.

The invention also relates to a process of preparing the formulations, in particular to the preparation of enteric tablets. Tablets may be produced by methods known in the art, e.g. thermal or melting and/or granulation processes and/or by compression processes or by combinations of these processes. In one embodiment, the tablet comprises a compressed matrix containing the modulator-compound.

The invention also relates to a process for the preparation of a pharmaceutical formulation, comprising the step of preparing a tablet or capsule containing at least one pyrazolopyrimidine compound of formula (I) (which is a negative allosteric modulator of the mGluR5 receptor) and then providing the tablet or capsule with at least one layer of an enteric coating, comprising a copolymer of methyl acrylate and methacrylic acid and/or a copolymer of ethyl acrylate and methacrylic acid.

Typical methods for the preparation thereof include the compression of granules prepared by wet or dry or melt granulation, and the direct compression of powder mixtures. Wet granulation involves the weighing of the active substances and the excipients, plus a

binder, mixing the ingredients, agglomerating them, screening them damp, drying them, dry screening, lubrication, and compressing the resultant admixture into tablets. Advantages of wet granulation include improvement of the cohesiveness and compressibility of powders, a good particle size distribution suitable for compression, reduction of dust and airborne contamination, and prevention of the segregation of components. In dry granulation, the ingredients are weighed, mixed and compacted, such as by roller compaction, and subsequently broken up or screened. The screened granules are lubricated and compressed into tablets. Since no liquid binder solution is used for agglomeration, the powder mixture which is granulated in dry form must comprise at least one dry binding agent such as microcrystalline cellulose, polyvinylpyrrolidone, or a co-processed mixture of lactose and microcrystalline cellulose.

One of the advantages of dry granulation methods is that they may be suitable for the processing of sensitive materials, such as moisture- or heat-sensitive ingredients, as no water is added during the process and no heating is required for drying the granules. Grades of microcrystalline cellulose are e.g. known under the trademark Avicel® such as Avicel PH 102.

In one embodiment, said solid matrix comprises one or several binders selected from starches, sugars, cellulose or modified cellulose such as microcrystalline cellulose or other cellulose derivatives, hydroxypropylcellulose, lactose, sugar alcohols such as xylitol, sorbitol, matitol. Binders also include gelatin and polyvinylpyrrolidone. In one embodiment, said solid matrix comprises one or several enteric polymers or release modifying or controlling polymers.

The formulations may also comprise further ingredients, such as untreated fumed silica. An appropriate grade is known under the trademark CAB-O-SIL®, such as CAB-O-SIL M5. In another embodiment, the solid matrix is prepared as a non-compressed matrix, e.g. by thermal or melt processing the ingredients intended to form said matrix. Subsequent to the preparation of the solid matrix comprising said active substance, said solid matrix is coated with said delayed-release excipient to form an enteric coating.

In one embodiment, said delayed-release excipient, in particular for the substituted pyrazolopyrimidine of formula (I), is selected from the group consisting of water-insoluble polymers, and/or water-swellaable polymers, and/or porous polymers. It is also possible to combine excipients from different chemical sub-groups.

Appropriate coating processes are known in the field of pharmaceutical sciences.

In one embodiment, the polymers used as delayed-release excipient may be provided as organic solutions, organic suspension organic dispersion, aqueous solution, aqueous suspension or aqueous dispersions and sprayed onto tablets using conventional coating equipment. Typically, the coating solution, suspension or dispersion will also contain one or more plasticizers, such as glycerol, propylene glycol, polyethylene glycol, diethyl phthalate, dibutyl phthalate, dibutyl sebacate, triacetin, triethyl citrate, acetyltriethyl citrate, acetyltributyl citrate, castor oil, mono- and diglycerides etc. In case the coating provides adhesive properties, at least a second layer of a polymer may be applied to said first coating that is capable preventing sticking. In some cases it is mandatory to place a primary, non functional sub-coating layer on the surface of the matrix formulation. This formulation concept is used, if e.g. the active ingredient interacts with excipients in the functional coating layer or the surface properties of the formulation are inappropriate for a direct coating of a functional coating.

In one embodiment, the delayed-release excipient is based on a polyacrylate or a polymethacrylate or on polyacrylate and/or polymethacrylate-copolymers, which optionally comprising ammonia acrylate moieties and/or ammonia methacrylate moieties. Suitable polymers are e.g. commercially available under the above referred trademarks such as Eudragit. Grades are e.g. EudragitL or S or FS, or combinations of two or more thereof. Accordingly, in one embodiment, the invention relates to a formulation comprising the active substance (modulator compound) and as delayed-release excipient a polyacrylate or a polymethacrylate or a polyacrylate copolymer and/or polymethacrylate copolymer, which optionally may contain ammonia acrylate moieties and/or ammonia methacrylate moieties, wherein said active agent is embedded or dispersed in a solid matrix, wherein said solid matrix is coated with said excipient.

In another embodiment, said tablet is coated with ethylcellulose. In one embodiment, a Surelease grade such as Surelease E-7-7050 is employed. In another embodiment, said tablet is coated with a hydroxypropyl methylcellulose (HPMC). Grades as defined above may be used, such as HPMC 2208, HPMC 2906 and HPMC 2910. In another embodiment, said tablet is coated with an ethylcellulose such a Surelease® grade as defined above, such as Surelease® E-7-7050. In another embodiment, said tablet is coated with a cellulose acetate. In one embodiment, one or two or more of the above mentioned polymers selected from ethylcellulose, hydroxypropyl methylcellulose, polyvinyl acetate/polyvinylpyrrolidone and cellulose acetate; may be used for the preparation of the coating.

Accordingly, in one embodiment, the invention relates to a pharmaceutical formulation comprising an active substance (which is a modulator compound) and as release-

controlling excipient one or more of the following: ethylcellulose; hydroxypropyl methylcellulose; polyvinyl acetate/polyvinylpyrrolidone; cellulose acetate. Said active substance often is embedded or dispersed in a solid matrix. Said solid matrix is coated with said delayed release excipient. In one embodiment, said release-controlling excipient
5 comprises talc or is employed in combination with talc or talcum powder.

Enteric coated tablets suitable for oral administration which contain the negative allosteric modulator of the mGluR5 receptor, in particular the substituted pyrazolopyrimidine of formula (I) (and in particular the compound used in Example 1 of this application), may be
10 prepared by conventional tableting techniques. For the preparation of the formulations of the present invention, the following polymers were found to be particularly useful for the enteric coating:

- methyl acrylate-methacrylic acid copolymers
- 15 • cellulose acetate succinate
- hydroxy propyl methyl cellulose phthalate
- hydroxy propyl methyl cellulose acetate succinate (hypromellose acetate succinate)
- polyvinyl acetate phthalate (PVAP)
- 20 • methyl methacrylate-methacrylic acid copolymers
- Shellac.

Also copolymers of methacrylic acid and ethyl acrylate are of particular interest.

Some favoured enteric polymers for the formulation of mGluR5 modulators, in particular
25 the substituted pyrazolopyrimidines of formula (I), are:

Cellulose Acetate Phthalate, also called Acetyl phthalyl cellulose; Aquacoat ; CAP; cellacephate; cellulose acetate benzene-1,2-dicarboxylate; cellulose acetate hydrogen 1,2-benzenedicarboxylate; cellulose acetate hydrogen phthalate; cellulose
30 acetate monophthalate; cellulose acetophthalate; cellulose acetylphthalate.

Cellulose acetate phthalate is cellulose in which about half the hydroxyl groups are acetylated, and about a quarter are esterified with one of two acid groups being phthalic acid, where the remaining acid group is free. Polyvinyl Acetate Phthalate
35 (Phthalavin[®] enteric coating polymer, PVAP), Sureteric[®], is a specially blended combination of, plasticizers and other ingredients in a completely optimized dry powder formulation. Designed as an alternative to acrylic polymer systems for

aqueous enteric coating of solid dosage forms, it provides consistent, reproducible enteric release profiles which ensures excellent product performance.

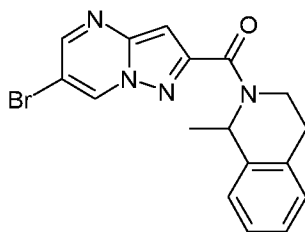
Poly(methacrylic acid-co-ethyl acrylate) 1:1 or Methacrylic Acid - Ethyl Acrylate Copolymer (1:1) Dispersion 30%, like Eudragit L and S, L 30 D-55, L 100-55 or FS 30 D.

Hypromellose acetate succinate, also called cellulose, 2-hydroxypropyl methyl ether, acetate, hydrogen butanedioate, also called HPMC – AS, also called Aqoat, is hypromellose with acetyl and succinoyl groups.

The following examples and patent claims further illustrate the invention. In the examples the manufacturing process for enteric coated tablets and hard capsules is described in detail.

Example 1 (Enteric tablet)

Preparation of an enteric formulation (tablet) comprising as negative allosteric modulator of the mGluR5 receptor the R-enantiomer of the compound (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone



(Ex1)

The respective amount of the active substance and appropriate types and amounts of excipients are weighed in, sieved, blended and compressed to core tablets. These excipients can be fillers, binders, flow promoters, disintegrants and glidants.

As one example, tablets can be made from compound (Example 1a):

Components/Excipients	mg
Pyrazolopyrimidine	100
Polyvinylpyrrolidone	10
Potato starch	20
Polyvinylpyrrolidone	19

Magnesium stearate	1
Microcrystalline Cellulose	50

As further example, tablets can be made from compound (Example 1b):

Components/Excipients	Mg
Pyrazolopyrimidine	100
Polyvinylpyrrolidone	19
Potato starch	20
Polyvinylpyrrolidone	10
Magnesium stearate	1
Microcrystalline Cellulose	50

- 5 These tablets (cores) are then coated with a dispersion of an enteric polymer. The dispersions can be aqueous based or co-solvent based or mixtures of both. If the dispersions are aqueous based, purified water according to pharmacopeial standards is used.
- 10 Typical cosolvents are ethanol, isopropanol and acetone. The dispersion can also be a mixture of different cosolvents with varying amounts of water. The dispersions can contain further functional excipients like plasticisers and pigments. The functional polymers can also be combined. To avoid the interaction of drug substances with the coating layer, a subcoating layer can be applied to the core tablets.

15

The enteric film is prepared, by the excipients Eudragit L 30 D – 55 (anionic methacrylate), Talc, Macrogol 6000 (Polyethylenglykol) and purified water. Depending on the surface of the core tablets and the batch size an enteric film coating layer with a thickness of 10 to 100 micrometer is applied to the core tablets.

20

A standard dispersion composition for such a coating process is described below:

Excipient / Component	Amount [g]
Eudragit L 30 D – 55	260
Talc	39
Macrogol 6000	16
Purified water	345
Total	660

For the application of the coating layer, a fluid bed coater or a pan coater are used. The coating layer can also be applied via hot melt coating.

Example 2 (Enteric hard capsule)

5

The respective amount of the above mentioned pyrazolopyrimidine and appropriate types and amounts of excipients are weighed in, sieved, blended and filled into hard capsules. These excipients can be filler, binder, flow promoter, disintegrants and glidants. The hard capsules consist either of gelatine, starch, carrageenan or cellulose derivatives like hypromellose or mixtures of these polymers or their derivatives.

10

The hard capsules are then coated with a dispersion of an enteric polymer. The dispersions can be aqueous based or cosolvent based or mixtures of both. If the dispersions are aqueous base, purified water according to pharmacopeial standards is used. Typical cosolvents are ethanol, isopropanol and acetone. The dispersion can also be a mixture of different cosolvents with varying amounts of water. The dispersions can contain further functional excipients like plasticisers and pigments.

15

The functional polymers can also be combined. To avoid leakages of the hard capsules a sub-coating layer can be applied to the hard capsules. These formulations with at least two layers have some advantages.

20

The enteric film is prepared, by the commercially available excipients Aqoat (HPMC – AS), Triethyl citrate, Talc, Sodium Lauryl Sulfate and purified water. Depending on the surface of the hard capsules and the batch size, an enteric film coating layer with a thickness of 50 to 250 micrometer is applied to the hard capsules. A standard dispersion composition for such a coating process is described below:

25

Excipient / Component	Amount [g]
Aqoat	70.0
Triethyl citrate	19.6
Talc	21.0
Sodium lauryl sulfate	2.1
Purified water	887.3
Total	1000.0

For the application of the coating layer fluid bed coater or pan coater are used. The coating layer can also be applied via hot melt coating.

Example 3 (Pharmacological testing)

5

With the specific pyrazolopyrimidine compound of Example 1, in a series of specific experiments, focussing on delay of gastric emptying, it was found that orally administered at a dose of e. g. 75 mg/kg (pharmacologically effective dose) of compound (Ex1), a marked and statistically significant increase in stomach content was observed in rats, suggesting a decrease in gastric emptying when compared to its vehicle (saline).

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Figure 1 shows on the left side the results of oral administration and on the right side the results of intraperitoneal administration.

15

On the other hand, the same specific pyrazolopyrimidine compound (of example 1) administered by the intraperitoneal route (systemic treatment) at a dose of e. g. 2.5 and 5 mg/kg (pharmacologically effective doses) of compound (Ex1) had no effect on gastric emptying. The responses of the pyrazolopyrimidine on gastric emptying in the rats were observed by measuring the content of the stomach after single intraperitoneal (i.p.) administration and after single oral (p.o.) administration.

20

Compounds which inhibit gastric emptying cause an increase in gastric content. Under the same conditions, the method-control compound (Atropine at 0.3 mg/kg, i.p.; 10 mg/kg, p.o.) was administered and a statistically significant decreases in gastric emptying was observed, supporting the validity of the method and the experimental conditions used. Followed by the local effect of a delayed gastric emptying, the transport and resorption of relevant medication e.g. L-Dopa is prolonged in the animals.

25

The further reference compound, Codeine at 10 mg/kg, i.p., also induced statistically significant decreases in gastric emptying.

30

Figure 1 shows the effect on gastric emptying in rats after oral and intraperitoneal application of the compound of example 1 and the control substances Atropine (at 10 mg/kg, p.o. and 0.3 mg/kg, i.p.). A significant delay of gastric emptying (increase of stomach content by 99%) can be seen after oral application of the pyrazolopyrimidine compound. This effect is comparable to the effect of the reference substance Atropine.

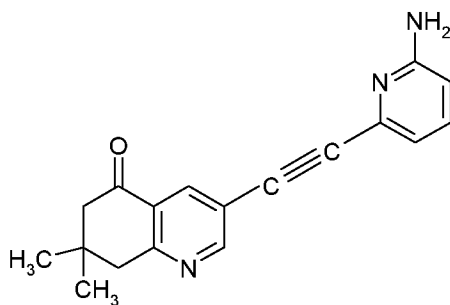
35

These results show that the effects observed on this parameter when the pyrazolopyrimidine was given orally were related to a local effect rather than a systemic effect. Therefore, by preparing a formulation of mGluR5-modulators (e.g. pyrazolopyrimidines of formula (I)) which does not release the compound into the stomach, a pharmaceutical benefit can be achieved.

Because of the small size of the rat's organs, the pyrazolopyrimidine was applied as compound per se, however, for bigger test animals (such as guinea pigs), enteric coated mini-tabletts containing the compound of Example 1 can be used to avoid stomach release and thereby avoid the delay of gastric emptying.

Example 4

Preparation of an enteric formulation comprising as negative allosteric modulator of the mGluR5 receptor the compound 7,7-Dimethyl-3-(6-amino-pyridine-2-yl-ethynyl)-7,8-dihydro-6H-quinolin-5-one.



A suitable formulation for a capsule containing 50 milligrams of the above mentioned active ingredient is as follows:

	Excipient / Component	mg
	Quinolinone	50
	Microcrystalline Cellulose	48
	Talcum	1
	Colloidal silicon dioxide	1

By using enteric coated mini-tabletts and bigger test animals, the local effect (in the stomach) can be avoided. This composition is then filled in a 0.8 ml gelatin capsule, which

then is coated with a layer of 200 micrometer of acrylic polymer (Eudragit L and/or Eudragit S).

Example 5 (Pharmacological testing)

5

In experiments with animals (rats), the pyrazolopyrimidine compound of example 1, the quinolinone-compound of example 4 and the known pyridine MTEP show that, when applied orally (with hydroxypropyl-methyl-cellulose and Polysorbate) have a local effect on gastric emptying.

10

Table 1 (Oral effect on gastric emptying)

Compound	Dose [mg/kg]	Effect [%]
Example 1 compound	75	+99
	75	+88
	75	+59
	500	+116
	2000	+152
Example 4 compound	25	+36
	75	+97
	150	+131
	300	+113
MTEP	10	+191
	20	+245

By using bigger test animals (guinea pigs), enteric coated mini-tablets containing the compound of example 1 can be applied, which do not release the drug compound into the stomach.

15

Example 6

A large number of mini-tablets, each comprising 5 mg of the R-enantiomer of (6-Bromopyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone are prepared from the following ingredients as follows.

20

Components/Excipients	mg
Pyrazolopyrimidine	5.0

Na-Carboxymethylcellulose EP	0.6
Silicium dioxide, Carbosil M5	0.2
Magnesium stearate, EP	0.3
Microcrystalline Cellulose,	13.9

For the preparation of this enteric formulation, the 5 mg of the active ingredient, and the amounts of microcrystalline cellulose (Avicel PH 102), sodium carboxymethylcellulose (Ac-Di-Sol) and silica (Cab-O-Sil M5) are weighted and blended. Magnesium stearate is weighed separately and added to the pre-blend.

For the final blend, a free fall blender (Bohle PTM 200) can be used.

Alternatively the appropriate amounts of the active ingredient, microcrystalline cellulose, sodium carboxymethylcellulose, silica, magnesium stearate are sieved before being blended. The powder (final blend) is compressed into biconvex tablets (core tablets) using a rotary tableting press applying main compression forces of approximately 10 to 20 kN. Each mini-tablet has a weight of (about) 20 mg.

An aqueous polymethacrylate dispersion is prepared from the following ingredients:

Excipient / Component	Amount [mg]
Eudragit L 30 D – 55	2.10
Talcum	1.05
Triethyl-citrate	0.21
<u>Total</u>	<u>3.36</u>

The aqueous polymethacrylate dispersion containing Eudragit® RS 30D-55 is then sprayed onto the small tablets. A thin layer of an enteric film (coating) was obtained.

After drying, each tablet contains:

5 mg	pyrazolopyrimidine,
13.9 mg	Avicel PH 102,
0.2 mg	Cab-O-Sil M5,
0.3 mg	magnesium stearate,
2.1 mg	polymethacrylate.
0.6 mg	Na-carboxymethylcellulose (Ac-Di-Sol),

1.05 talkum
0.21 triethylcitrate.

The diameter of each coated tablet is 2.1 mm (longest diameter). The tablets are tested with respect to the drug release over time for the modulator of the mGluR5 receptor (6-Bromo-pyrazolo[1,5-a]-pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone in a dissolution tester using the gastric dissolution medium (simulated gastric fluid).

Example 7 (Pharmacological testing)

For this testing, a coated tablet containing an amount of 5 mg (or a multitude of coated granules or mini-tablets) of the pyrazolopyrimidine is suspended in 750 ml of an acidic solution (SGF) at pH 1.2 After stirring with paddles for 2 hours at 100 rpm, not more than 10 %, in particular not more than 5 %, of the active ingredient is released. The dissolution medium is adjusted with phosphate buffer to pH 6.8. This pH-change takes about 2 minutes. The further drug release is observed:

After 2 minutes of buffer change, a sample is taken and no more than 10 % of the pyrazolopyrimidine is released.

After stirring with baskets for 17 (2 + 15) minutes at 100 rpm, 35 % of the active agent is released.

After stirring with baskets for 32 (30+2) minutes at 100 rpm, 52 % of the active agent is released.

After stirring with baskets for 47 (45+2) minutes at 100 rpm, 64 % of the active agent is released.

After stirring with baskets for 62 minutes (60+2) at 100 rpm, 72 % of the active agent is released.

Example 8 (Preparation of mini-tablets)

As further formulations, enteric mini-tablets can be prepared from the pyrazolopyrimidine of Example 1 and the following components. Firstly, the core of the mini-tablets is prepared which then is enteric coated.

Formulation 8a)

Excipient / Component	Amount per dosage form [mg]
Pyrazolopyrimidine of Example 1	2.5

Cellulose, microcrystalline	2.32
Silicon dioxide	0.06
Magnesium stearate	0.12
Total core tablet weight [g]	5 mg
Eudragit L 30 D 55 (dry mass)	1.05
Triethyl citrate	0.105
Talc	0.525
Total coating weight	1.68
Weight per dosage form	6.68 mg/ enteric film coated mini-tablet

As further formulations, enteric mini-tablets can be prepared from the pyrazolopyrimidine of Example 1 and the following components:

5 Formulation 8b)

Excipient / Component	Amount per dosage form [mg]
Pyrazolopyrimidine	1.0
Cellulose, microcrystalline	1.88
Silicon dioxide	0.06
Magnesium stearate	0.06
Total core tablet weight [g]	3 mg / tablet
Eudragit L 30 D 55 (dry mass)	1.05
Triethyl citrate	0.105
Talc	0.525
Total coating weight	1.68
Weight per dosage form	4.68 mg/ enteric film coated mini tablet

As further formulations, enteric mini-tablets can be prepared from the pyrazolopyrimidine of Example 1 and the following components:

10

Formulation 8c)

Excipient / Component	Amount per dosage form [mg]
Pyrazolopyrimidine	2.5
Cellulose, microcrystalline	2.32

Silicon dioxide	0.06
Magnesium stearate	0.12
Total core tablet weight [g]	5 mg
Aquoat (AS MF)	1.75
Triethyl citrate	0.49
Talc	0.525
Sodium lauryl sulphate	0.0525
Water	q.s.
Total coating weight	2.8175
Weight per dosage form	7.8175 mg/ enteric film coated mini tablet

As further formulations, enteric mini-tablets can be prepared from the pyrazolopyrimidine of Example 1 and the following components:

5 Formulation 8d)

Excipient / Component	Amount per dosage form [mg]
Pyrazolopyrimidine	1.0
Eudragit L 100	2.82
Cellulose, microcrystalline	1.0
Silicon dioxide	0.06
Magnesium stearate	0.12
Total tablet weight [g]	5 mg / enteric film coated mini tablet

As further formulations, enteric mini-tablets can be prepared from the pyrazolopyrimidine of Example 1 and the following components:

10

Formulation 8e)

Excipient / Component	Amount per dosage form [mg]
Pyrazolopyrimidine	1.0
Eudragit S 100	2.82
Cellulose, microcrystalline	1.0
Silicon dioxide	0.06
Magnesium stearate	0.12
Total tablet weight [g]	5 mg / enteric film coated mini tablet

Example 9 (Preparation of enteric granules)

As further formulations, small enteric granules can be prepared from the pyrazolo-pyrimidine of Example 1 and the following components:

5

Formulation 9a)

Excipient / Component	[mg]
Pyrazolopyrimidine	1.0
Eudragit S 100*	1.0
Calcium phosphate	1.0

* applied as organic or aqueous solution (Eudragit S 12.5 or Eudragit FS 30 D) in a fluid bed or other conventional granulation equipment

10

As further formulations, small enteric granules can be prepared from the pyrazolo-pyrimidine of Example 1 and the following components:

15 Formulation 9b)

Excipient / Component	[mg]
Pyrazolo-pyrimidine	2.0
Eudragit L 100*	1.0
Cellulose, microcrystalline	0.5

* applied as organic solution (Eudragit L 12.5) in a fluid bed or conventional granulation equipment

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As further formulations, small enteric granules can be prepared from the pyrazolo-pyrimidine of Example 1 and the following components:

Formulation 9c)

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Excipient / Component	[mg]
Pyrazolo-pyrimidine	q.s.
Aquoat (AS MF)	7.0
Triethyl citrate	1.96

Talc	2.1
Sodium lauryl sulphate	0.21
Water	q.s.

The pyrazolo-pyrimidine is granulated in a fluid bed or a conventional granulator with the enteric granulation fluid.

5 Example 10 (Preparation of pellets)

As further formulations, small pellets can be prepared from the pyrazolo-pyrimidine of Example 1 and the following components:

10 Formulation 10a)

Excipient / Component	[mg]
Sugar spheres	q.s.
Pyrazolo-pyrimidine	10 mg
Aquoat (AS MF)	7.0
Triethyl citrate	1.96
Talc	2.1
Sodium lauryl sulphate	0.21
Water	q.s.

The pyrazolo-pyrimidine is dispersed homogeneously in the Aquoat/excipient dispersion and sprayed on the sugar spheres. As further formulations, small pellets can be prepared

15 from the pyrazolo-pyrimidine of Example 1 and the following components:

Formulation 10b)

Excipient / Component	[mg]
Sugar spheres	q.s.
Pyrazolo-pyrimidine	10 mg
Eudragit L 30 D 55 (dry mass)	7.0
Triethyl citrate	1.96
Talc	2.1

The pyrazolo-pyrimidine is dispersed homogeneously in the aqueous Eudragit L 30 D 55/excipient dispersion and sprayed on the sugar spheres.

As further formulations, small pellets can be prepared from the pyrazolo-pyrimidine of Example 1 and the following components:

Formulation 10c)

Excipient / Component	[mg]
Cellulose spheres	q.s.
Pyrazolo-pyrimidine	1 mg
Eudragit S 12.5 % organic solution	7.0
Triethyl citrate	1.96
Talc	1.1

The pyrazolo-pyrimidine is dispersed homogeneously in the organic Eudragit dispersion and sprayed on the sugar spheres.

As further formulations, small pellets can be prepared from the pyrazolo-pyrimidine of Example 1 and the following components:

Formulation 10d)

Excipient / Component	[mg]
Cellulose spheres	q.s.
Pyrazolo-pyrimidine	1 mg
Hypromellose	1 mg
Water	q.s.
Eudragit S 12.5 % organic solution	3.5
Triethyl citrate	0.98
Talc	0.55

The pyrazolo-pyrimidine is dispersed homogeneously in the aqueous HPMC solution and sprayed onto the cellulose spheres. The organic Eudragit dispersion is sprayed on top as a second layer.

Example 11 (Preparation of multi-particular formulation)

As further formulations, enteric mini-particles (tablets) can be prepared from the pyrazolopyrimidine of Example 1 and the following components:

Excipient / Component	Amount of dosage form [mg]
Pyrazolopyrimidine	5.0
Cellulose, microcrystalline, Avicel PH 302	13.9
Croscarmellose sodium	0.6
Silicon dioxide, Carbosil M5	0.2
Magnesium stearate	0.3
Total core tablet weight [g]	20 mg / tablet
Eudragit L 100-55 (dry mass)	2.1
Triethyl citrate	0.21
Talc	1.05
Total coating weight	3.36
Weight per dosage form	23.36 mg / enteric film coated mini-particle

- 5 5 mg of the active ingredient of Example 1 and the amounts mentioned of the further components are weighted and then blended. The powder is compressed into small mini-tablets. These mini-tablets have a weight of 20 mg each. The mini-tablets are then enteric coated with an aqueous dispersion containing Eudragit L 100-55. In this dispersion the above mentioned further additives are used.

10

For the further testing, the dissolution characteristics of the enteric coated mini-tablets were studied. In three different experiments, several of the coated mini-tablets are tested in a dissolution tester with the paddle apparatus for several hours in water (SGF-water, at pH 1.2) at room temperature.

15

It was found that for periods of two hours, four hours and eight hours, no release of the active ingredient from the mini-tablet was observed (less than 1 % by weight). This test demonstrated that the enteric coated mini-tablets do not release the pyrazolopyrimidin compound under such acidic conditions (as in the human stomach) for up to 8 hours.

20

After a respective period of time (2h, 4h or 8h), the pH was changed (within 2 minutes) to pH 6,8.

It was observed that in all experiments with the coated mini-tablets,

25

- a) 15 minutes after the pH change, more than 50% of the active ingredient (pyrazolopyrimidine) was released from the mini-tablets,
- b) 30 minutes after the pH change, more than 75% of the active ingredient was released from the mini-tablets.

For the further testing of the mini-tablets comprising the pyrazolopyrimidin compound of example 1 and an enteric coating as described above, the mini-tablets were used in clinical studies performed with 18 healthy human volunteers.

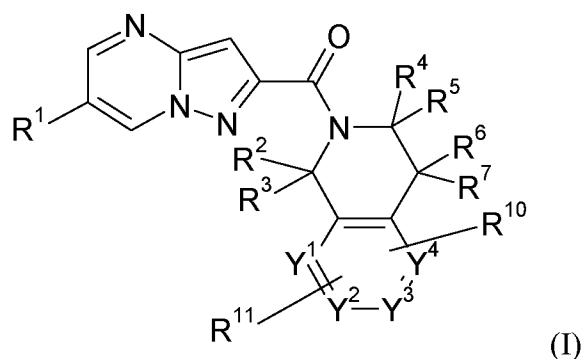
As one results of this clinical study, it was observed that the mini-tablets containing the enteric coated pyrazolopyrimidin could be applied and swallowed very easily, the mini-tablets were well tolerated and the volunteers after oral application of the mini-tablets showed no delayed emptying of the gastric system.

For commercial applications, the mini-tablets described in example 11 can be filled into small bags or stick packs. For example, 24 mini-tablets, each comprising 5 mg of active compound, lead to an applicable dose of 120 mg of the pyrazolopyrimidin. The mini-tablets can be filled into small bags which can then be orally applied to the volunteer or patient.

Patent Claims

- 5 1. Pharmaceutical formulation, comprising at least one negative allosteric modulator of the mGluR5 receptor and at least one layer of enteric coating, where the components of the enteric coating are chosen that the pharmaceutical formulation releases the negative allosteric modulator of the mGluR5 receptor in the small and/or large intestine.
- 10 2. Pharmaceutical formulation according to claim 1, where the pharmaceutical comprises 1 to 800 mg of a negative allosteric modulator compound and at least one layer of an enteric polymer coating which is resistant to gastric acids, wherein the negative allosteric modulator of the mGluR5 receptor is in the form of a
- 15 multiple unit dosage form.
3. Pharmaceutical formulation according to claim 1 or claim 2, comprising an enteric tablet or enteric capsule, having an enteric polymer coating with a thickness of 5 to 900 micrometer.
- 20 4. Pharmaceutical formulation according to one of the claims 1 to 3, comprising an enteric polymer coating which is resistant to gastric acids for at least 4 hours, preferably at least 24 hours, but which allows at least 50 % of the negative allosteric modulator compound to be released from the formulation at a pH of 6.8 or higher within 60 minutes.
- 25 5. Pharmaceutical formulation according to one of the claims 1 to 4, comprising as negative allosteric modulator of the mGluR5 receptor a compound from the group comprising pyrazolo[1,5-a]pyrimidines, tetrahydroquinolinones, fused pyridines, ethinyl-substituted fused pyridines, ethinyl-substituted tetrahydroquinolones, phenyl-ethinyl-substituted heterocyclic compounds or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof.
- 30 6. Pharmaceutical formulation according to one of the claims 1 to 5, comprising as negative allosteric modulator of the mGluR5 receptor a pyrazolo[1,5-a]pyrimidine
- 35

compound of formula (I) or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof,



wherein,

Y¹ represents N or C-,

Y² represents N or C-,

Y³ represents N or C-,

Y⁴ represents N or C-,

where at least two of the groups Y¹ to Y⁴ denote a carbon atom,

R¹ represents chloro or bromo;

R² and R³ each independently represent hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl or trifluoromethyl; or

R² and R³ both together with the carbon atom of the ring represent a carbonyl group;

R⁴ and R⁵ each independently represent hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl or trifluoromethyl; or

R⁴ and R⁵ both together with the carbon atom of the ring represent a carbonyl group;

R⁶ and R⁷ independently represent hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl or trifluoromethyl; or R⁶ and R⁷ both together with the carbon atom of the ring represent a carbonyl group;

R² or R³ together with R⁶ and R⁷ may also form a bivalent radical from the group CH₂-CH₂ or CH₂-O;

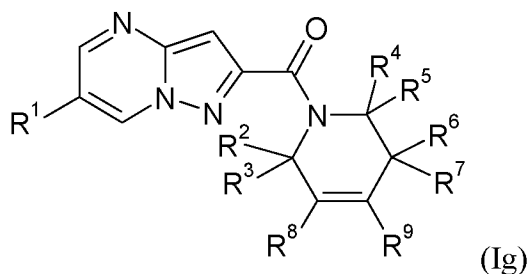
R¹⁰ and R¹¹ independently represent hydrogen, halogen, amino, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, aryl, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, C₃₋₇-cycloalkyloxy, C₂₋₆alkenyloxy, C₂₋₆alkynyloxy, heteroaryl, heterocyclyl, aryloxy, heteroaryloxy, heterocyclyloxy, C₁₋₆alkylamino, di-C₁₋₆alkylamino, C₃₋₇-cycloalkylamino, di-C₃₋₇-cycloalkylamino, C₁₋₆alkyl-C₃₋₇-cycloalkylamino, C₂₋₆alkenylamino, C₂₋₆alkynylamino, di-C₂₋

₆alkenylamino, di-C₂₋₆alkynylamino, C₁₋₆alkyl-C₂₋₆-alkenylamino, C₁₋₆alkyl-C₂₋₆-alkynylamino, C₂₋₆alkenyl-C₃₋₇-cycloalkylamino, C₂₋₆alkynyl-C₃₋₇-cycloalkylamino, C₂₋₆alkenyl-C₂₋₆-alkynylamino arylamino, diarylamino, aryl-C₁₋₆alkylamino, aryl-C₂₋₆alkenylamino, aryl-C₂₋₆alkynylamino, aryl-C₃₋₇-cycloalkylamino, heteroarylamino, diheteroarylamino, heteroaryl-C₁₋₆alkylamino, heteroaryl-C₂₋₆alkenylamino, heteroaryl-C₂₋₆alkynylamino, heteroaryl-C₃₋₇-cycloalkylamino, heteroarylarylamino, heterocyclylamino, diheterocyclylamino, heterocyclyl-C₁₋₆alkylamino, heterocyclyl-C₂₋₆alkenylamino, heterocyclyl-C₂₋₆alkynylamino, heterocyclyl-C₃₋₇-cycloalkylamino, heterocyclylarylamino, heterocyclylhetero-arylamino, acyl, acyloxy, acylamino, C₁₋₆alkoxycarbonyl, C₃₋₇-cycloalkoxy-carbonyl, C₂₋₆alkenyloxycarbonyl, C₂₋₆alkynyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, heterocyclyloxycarbonyl, aminocarbonyl, C₁₋₆alkylamino-carbonyl, di-C₁₋₆alkylaminocarbonyl, C₃₋₇-cycloalkylaminocarbonyl, di-C₃₋₇-cycloalkylaminocarbonyl, C₁₋₆alkyl-C₃₋₇-cycloalkylaminocarbonyl, C₂₋₆alkenyl-aminocarbonyl, C₂₋₆alkynylaminocarbonyl, di-C₂₋₆alkenylaminocarbonyl, di-C₂₋₆alkynylaminocarbonyl, C₁₋₆alkyl-C₂₋₆-alkenylaminocarbonyl, C₁₋₆alkyl-C₂₋₆-alkynyl-aminocarbonyl, C₂₋₆alkenyl-C₃₋₇-cycloalkylaminocarbonyl, C₂₋₆alkynyl-C₃₋₇-cycloalkylaminocarbonyl, C₂₋₆alkenyl-C₂₋₆-alkynylaminocarbonyl, arylaminocarbonyl, diarylamino-carbonyl, aryl-C₁₋₆alkylaminocarbonyl, aryl-C₂₋₆alkenylaminocarbonyl, aryl-C₂₋₆alkynylaminocarbonyl, aryl-C₃₋₇-cycloalkylaminocarbonyl, heteroarylaminocarbonyl, diheteroarylaminocarbonyl, heteroaryl-C₁₋₆alkylaminocarbonyl, heteroaryl-C₂₋₆alkenylaminocarbonyl, heteroaryl-C₂₋₆alkynylaminocarbonyl, heteroaryl-C₃₋₇-cycloalkylaminocarbonyl, heteroarylarylamino-carbonyl, heterocyclylaminocarbonyl, diheterocyclylaminocarbonyl, heterocyclyl-C₁₋₆alkylaminocarbonyl, heterocyclyl-C₂₋₆alkenylaminocarbonyl, heterocyclyl-C₂₋₆alkynylaminocarbonyl, heterocyclyl-C₃₋₇-cycloalkylaminocarbonyl, heterocyclylarylamino-carbonyl, heterocyclylheteroarylamino-carbonyl, C₁₋₆alkylsulfinyl, C₃₋₇-cycloalkylsulfinyl, C₂₋₆alkenylsulfinyl, C₂₋₆alkynylsulfinyl, arylsulfinyl, heteroarylsulfinyl, heterocyclylsulfinyl, C₁₋₆alkylsulfonyl, C₃₋₇-cycloalkylsulfonyl, C₂₋₆alkenylsulfonyl, C₂₋₆alkynylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heterocyclylsulfonyl, C₁₋₆alkylsulfonylamino, or arylsulfonylamino;

or R¹⁰ and R¹¹ together with the two carbon atoms carrying them represent a heteroaryl having 5 or 6 ring members or a heterocyclyl group having 5 or 6 ring members, which can be substituted by one of the following groups: halogen,

hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl and C₁₋₆alkoxy, in particular by methyl.

7. Pharmaceutical formulation according to one of the claims 1 to 6, comprising as negative allosteric modulator of the mGluR5 receptor a pyrazolo[1,5-a]pyrimidine compound of formula (Ig) or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof,



wherein

R¹ represents chloro or bromo;

R², R³, R⁴, R⁵, R⁶ and R⁷, which may be the same or different, each independently represent hydrogen, C₁₋₆alkyl, amino, hydroxy, halogen, or trifluoromethyl;

R⁸ and R⁹ together with the carbon atoms to which they are attached may form an unsaturated cyclic ring system containing 5 to 7 (i.e. 5, 6 or 7) carbon atoms, wherein 0 to 4 (i.e. 0, 1, 2, 3 or 4) of the carbon atoms of the ring system formed by R⁸ and R⁹ may be replaced by heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the ring system may be optionally substituted by one or more (e.g., 1, 2, or 3) substituents, which may be the same or different, independently selected from halogen, amino, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, aminocarbonyl, N-C₁₋₆alkylaminocarbonyl, di-N,N-C₁₋₆alkylaminocarbonyl, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, C₁₋₆alkoxycarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkylamino, di-C₁₋₆alkylamino, C₁₋₆alkylcarbonylamino, C₁₋₆alkylenedioxy, aryl, heteroaryl, heterocyclyl, and cycloC₃₋₁₂alkyl.

8. Pharmaceutical formulation according to one of the claims 1 to 7, comprising as negative allosteric modulator of the mGluR5 receptor a pyrazolo[1,5-a]pyrimidine compound of formula (Ig) or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof, wherein the radicals denote:

R¹ represents chloro or bromo;

R^2 , R^3 , R^4 , R^5 , R^6 and R^7 , which may be the same or different, each independently represent hydrogen, C_{1-6} alkyl, amino, hydroxy, halogen, or trifluoromethyl;

R^8 and R^9 together with the carbon atoms to which they are attached may form an unsaturated cyclic ring system containing 5 to 7 carbon atoms, wherein 0 to 4 of the carbon atoms of the ring system formed by R^8 and R^9 may be replaced by heteroatoms independently selected from nitrogen, oxygen and sulfur and wherein the ring system may be optionally substituted by one or more substituents, which may be the same or different, independently selected from halogen, amino, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, aminocarbonyl, $N-C_{1-6}$ alkylaminocarbonyl, di- $N,N-C_{1-6}$ alkylaminocarbonyl, C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonyloxy, C_{1-6} alkylamino, di- C_{1-6} alkylamino, C_{1-6} alkylcarbonylamino, C_{1-6} alkylenedioxy, aryl, heteroaryl, heterocyclyl, and cyclo C_{3-12} alkyl.

9. Pharmaceutical formulation according to one of the claims 1 to 8, comprising as negative allosteric modulator of the mGluR5 receptor a pyrazolo[1,5-a]pyrimidine or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph of the following compounds:

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-hydroxy-7-methoxy-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3,3-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3,3-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3,4-dihydro-1H-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dimethoxy-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 5 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dimethoxy-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-hydroxy-7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-hydroxy-7-methoxy-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 10 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dimethoxy-3-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dimethoxy-3-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 15 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dimethoxy-3,3-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dimethoxy-3,3-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-5,8-dihydro-6H-[1,7]naphthyridin-7-yl)-methanone
- 20 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-5,8-dihydro-6H-[1,7]naphthyridin-7-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-[2,7]naphthyridin-2-yl)-methanone
- 25 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-[2,7]naphthyridin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-[2,6]naphthyridin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-[2,6]naphthyridin-2-yl)-methanone
- 30 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-methyl-7,8-dihydro-5H-[1,6]naphthyridin-6-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-methyl-7,8-dihydro-5H-[1,6]naphthyridin-6-yl)-methanone
- 35 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3,4-dihydro-1H-isoquinolin-2-yl)-methanone

- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-fluoro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-fluoro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone;
- 5 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-fluoro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone;
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-fluoro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-fluoro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 10 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-fluoro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-fluoro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 15 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-fluoro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-fluoro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-fluoro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 20 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-fluoro-1-ethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-fluoro-1-ethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 25 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-fluoro-1-ethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-fluoro-1-ethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-fluoro-1-ethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 30 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-fluoro-1-ethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-fluoro-1-ethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 35 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-fluoro-1-ethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-fluoro-1-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-fluoro-1-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-fluoro-1-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 5 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-fluoro-1-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-fluoro-1-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-fluoro-1-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 10 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-fluoro-1-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-fluoro-1-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 15 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-ethyl-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-((R)-3-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-((S)-3-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 20 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (7-Bromo-3,4-dihydro-1H-isoquinolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
- 25 (7-Bromo-3,4-dihydro-1H-isoquinolin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-fluoro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,4-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 30 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,4-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,4-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 35 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,4-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,4-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,4-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-methoxy-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 5 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-methoxy-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromopyrazolo[1,5-a]pyrimidin-2yl)-(1-ethyl-3,4-dihydro-1H-isoquinolin-2-yl)methanone
- (6-Bromopyrazolo[1,5-a]pyrimidin-2yl)-(1-isopropyl-3,4-dihydro-1H-isoquinolin-2-yl)methanone
- 10 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-isopropyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-ethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 15 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (7-Bromo-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
- 20 (7-Bromo-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-cyclohexyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 25 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-cyclohexyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-propyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-((S)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone;
- 30 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-((R)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone;
- (5-Bromo-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
- 35 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-5-methoxy-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (5-Bromo-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-pyridin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-methoxy-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 5 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-methoxy-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5,6-dimethoxy-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 10 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5,8-difluoro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(5,8-difluoro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 15 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-5-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-5-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-methyl-7,8-dihydro-5H-[1,6]naphthyridin-6-yl)-methanone
- 20 (3-Bromo-7,8-dihydro-5H-[1,6]naphthyridin-6-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyridin-3-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 25 (3-Bromo-7,8-dihydro-5H-[1,6]naphthyridin-6-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-pyridin-3-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-isoquinoline-7-carbonitrile
- 30 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-pyridin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-nitro-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 35 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-nitro-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-pyrimidin-5-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-morpholin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-morpholin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 5 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-morpholin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-morpholin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-morpholin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 10 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-morpholin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-morpholin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 15 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-morpholin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyrimidin-5-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-5-pyrimidin-5-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 20 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-5-pyrimidin-3-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (3-Bromo-7,8-dihydro-5H-[1,6]naphthyridin-6-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
- 25 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,5-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 30 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,7-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,7-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 35 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,5-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (7-Chloro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone

- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-chloro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (5-Chloro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone
- 5 N-[2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-acetamide
- N-[2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-isoquinolin-5-yl]-acetamide
- 10 N-[2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-isoquinolin-5-yl]-acetamide
- N-[2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-isoquinolin-5-yl]-acetamide
- N-[2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-isoquinolin-5-yl]-acetamide
- 15 2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-isoquinoline-5-carboxylic acid dimethylamide
- 2-(6-Chloro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-isoquinoline-5-carboxylic acid dimethylamide
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-2,3,5,8-tetrahydro-6H-1,4-dioxo-7-aza-phenanthren-7-yl)-methanone
- 20 2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-isoquinoline-5-carbonitrile
- 2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydro-isoquinoline-7-carbonitrile
- 25 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyridin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyridin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyridin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 30 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-pyridin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-methyl-8,9-dihydro-6H-[1,3]dioxolo[4,5-f]isoquinolin-7-yl)-methanone
- 35 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-5-pyridin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-5-pyridin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

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

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

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

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

10 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-pyridin-2-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

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

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

15 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-pyridin-2-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

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

20 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[5-(2,4-dimethoxy-pyrimidin-5-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone

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

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

25 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[5-(6-fluoro-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone

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

30 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[5-(2-methoxy-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone

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

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

35 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[5-(6-methoxy-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone

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

- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[6-(2-methoxy-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[6-(2-fluoro-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 5 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[6-(2-fluoro-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[6-(6-fluoro-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[6-(6-fluoro-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 10 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[6-(2,6-dimethoxy-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[6-(2,6-dimethoxy-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 15 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[6-(2,4-dimethoxy-pyrimidin-5-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[6-(2,4-dimethoxy-pyrimidin-5-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[7-(6-methoxy-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 20 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[7-(2-methoxy-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[7-(2,4-dimethoxy-pyrimidin-5-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 25 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[7-(2,4-dimethoxy-pyrimidin-5-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[7-(2-fluoro-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[7-(2-fluoro-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 30 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[5-(2-fluoro-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-[5-(2-fluoro-pyridin-3-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 35 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-furan-2-yl-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-furan-2-yl-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-furan-2-yl-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-furan-2-yl-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 5 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-8-(5-methyl-furan-2-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-7-(5-methyl-furan-2-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-6-(5-methyl-furan-2-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 10 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-5-(5-methyl-furan-2-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-furan-3-yl-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 15 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-furan-3-yl-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-furan-3-yl-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-furan-3-yl-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 20 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[8-(3,5-dimethyl-isoxazol-4-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[7-(3,5-dimethyl-isoxazol-4-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 25 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[6-(3,5-dimethyl-isoxazol-4-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[5-(3,5-dimethyl-isoxazol-4-yl)-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-8-(1H-pyrazol-4-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 30 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-7-(1H-pyrazol-4-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-6-(1H-pyrazol-4-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 35 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-5-(1H-pyrazol-4-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-8-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone

- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-7-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 5 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-5-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-8-(3-methyl-1H-pyrazol-4-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-7-(3-methyl-1H-pyrazol-4-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 10 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-6-(3-methyl-1H-pyrazol-4-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-5-(3-methyl-1H-pyrazol-4-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 15 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-8-(2H-tetrazol-5-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-7-(2H-tetrazol-5-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-6-(2H-tetrazol-5-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 20 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-5-(2H-tetrazol-5-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-[2,7]naphthyridin-2-yl)-methanone
- 25 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-[2,6]naphthyridin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-methyl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-5,8-dihydro-6H-pyrido[3,4-d]pyrimidin-7-yl)-methanone
- 30 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-5-nitro-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-nitro-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 35 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-nitro-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-8-nitro-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-5-nitro-3,4-dihydro-1H-[2,7]naphthyridin-2-yl)-methanone
2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-isoquinoline-5-carbonitrile
- 5 2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-isoquinoline-5-carboxylic acid methyl ester
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(2,6-dimethyl-8,9-dihydro-6H-3-oxa-1,7-diaza-cyclopenta[a]naphthalen-7-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(4-methyl-1,4-dihydro-2H-
- 10 [3,7]phenanthrolin-3-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(2,6-dimethyl-8,9-dihydro-6H-thiazolo[4,5-f]isoquinolin-7-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-methanesulfonyl-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 15 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-methanesulfonyl-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-methanesulfonyl-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methanesulfonyl-1-methyl-3,4-
- 20 dihydro-1H-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(4,7-dimethyl-1,4,7,8,9,10-hexahydro-2H-[3,7]phenanthrolin-3-yl)-methanone
1-[2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-isoquinolin-5-yl]-ethanone
- 25 2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-isoquinoline-6-carboxylic acid methyl ester
2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydro-isoquinoline-7-carboxylic acid methyl ester
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-5-(morpholine-4-carbonyl)-
- 30 3,4-dihydro-1H-isoquinolin-2-yl]-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-7-(morpholine-4-carbonyl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-6-(morpholine-4-carbonyl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone
- 35 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-methyl-8,9-dihydro-6H-furo[3,2-f]isoquinolin-7-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3,6-dimethyl-3,6,8,9-tetrahydro-pyrrolo[3,2-f]isoquinolin-7-yl)-methanone

- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-5,8-dihydro-6H-furo[3,2-g]isoquinolin-7-yl)-methanone
- 7-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-2,6-dimethyl-1,2,6,7,8,9-hexahydro-pyrrolo[3,4-f]isoquinolin-3-one
- 5 7-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-2,6-dimethyl-2,3,6,7,8,9-hexahydro-pyrrolo[3,4-f]isoquinolin-1-one
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-diethylamino-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-diethylamino-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 10 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-diethylamino-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-diethylamino-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 15 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-difluoro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-difluoro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dichloro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 20 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dichloro-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dibromo-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 25 (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dibromo-1-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-morpholin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-morpholin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 30 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-8-morpholin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-8-morpholin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- 35 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-morpholin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
- (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-morpholin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

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

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

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

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

10 (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-pyrrolidin-1-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

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

10. 15 Pharmaceutical formulation according to one of the claims 1 to 9, comprising the negative allosteric modulator of the mGluR5 receptor in the form of a multiple unit dosage form which is a mini-tablet.

11. 20 Process for the preparation of a pharmaceutical formulation according to one of the claims 1 to 10, comprising the step of preparing a tablet or capsule containing at least one negative allosteric modulator of the mGluR5 receptor and then providing the tablet or capsule with at least one layer of an enteric coating.

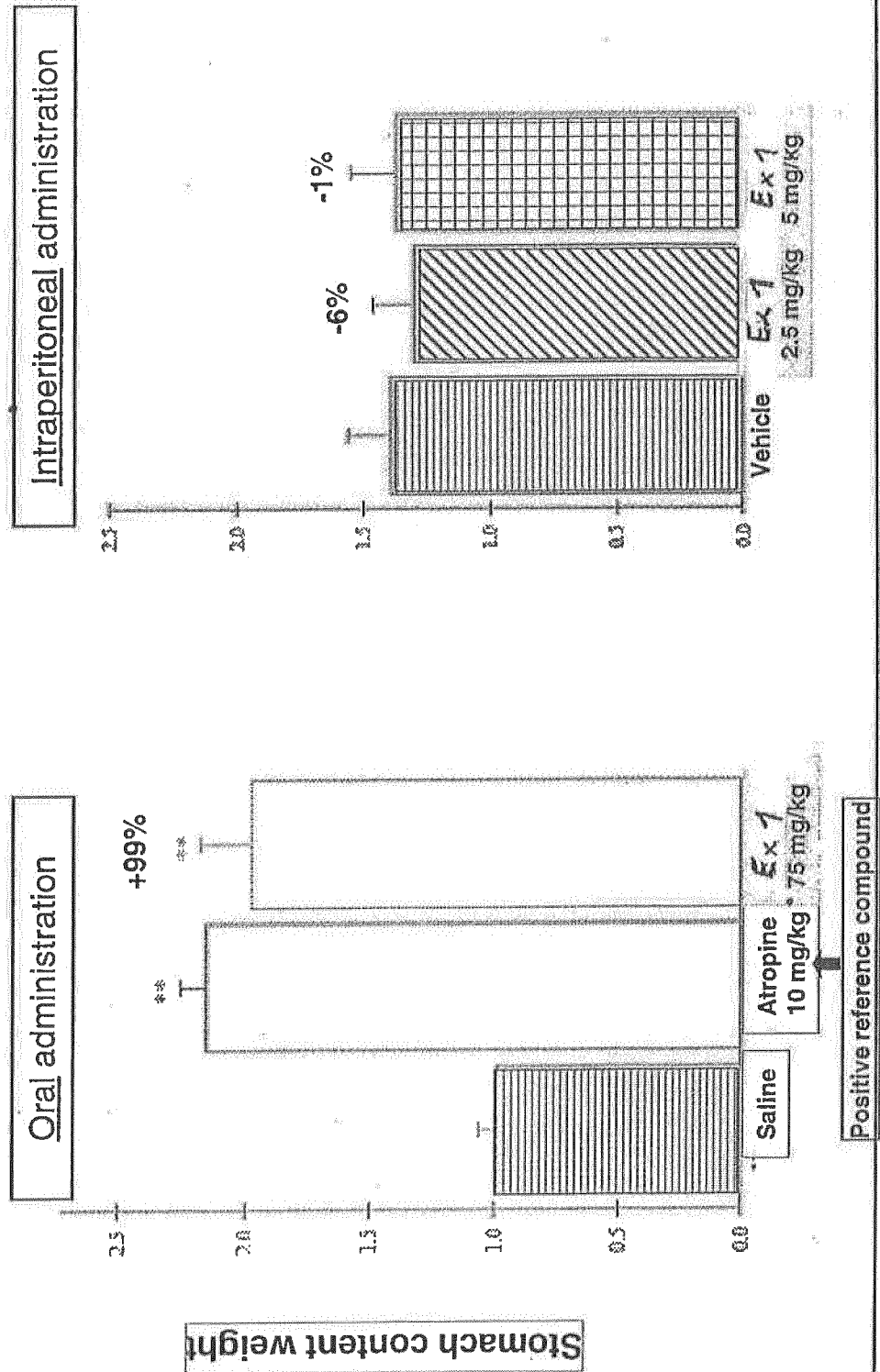
12. 25 Process for the preparation of a pharmaceutical formulation according to claim 11, comprising the step of preparing a tablet or capsule containing at least one pyrazolopyrimidine compound of formula (I) which is a negative allosteric modulator of the mGluR5 receptor and then providing the tablet or capsule with at least one layer of an enteric coating comprising a copolymer of methyl acrylate and methacrylic acid and/or a copolymer of ethyl acrylate and methacrylic acid.

30 13. Formulation according to one of the claims 1 to 10 for use for the treatment or prevention of a condition or disease from the following: Alzheimer's disease, Parkinson's disease, Parkinson's dementia, mild cognitive impairment, L-dopa-induced dyskinesias (LID), L-dopa-induced dyskinesias in Parkinson's disease, dyskinesias, drug induced dyskinesias, dopaminomimetic-induced dyskinesias, 35 tremor, anxiety disorders, social anxiety disorder (SAD), dementia, dementia in Alzheimer's disease, major depressive disorder, depression, migraine, movement disorders, pain, chronic pain, neuropathic pain and gastroesophageal reflux disease (GERD).

14. Formulation according to one of the claims 1 to 10 for use for the treatment or prevention of Parkinson's disease, Parkinson's dementia, L-dopa-induced dyskinesias (LID), L-dopa-induced dyskinesias in Parkinson's disease, dyskinesias, drug induced dyskinesias, dopaminomimetic-induced dyskinesias, tremor, anxiety disorders, depression, migraine, chronic pain, neuropathic pain and gastroesophageal reflux disease (GERD).
- 5
15. A pharmaceutical formulation according to any one of the claims 1 to 10 comprising at least two different active substances, which contains at least one a negative allosteric modulator of the mGluR5 receptor and at least one active substance from the group:
- 10
- Levo-Dopa, Carbidopa, Benserazid,
L-Serine-2-(2,3,4-trihydroxy-benzyl)-hydrazide,
15 L-Tyrosine-2-(2,3,4-trihydroxy-benzyl)-hydrazide and
Glycine-2-(2,3, 4-trihydroxy-benzyl)-hydrazide.

Fig. 1

Gastric emptying after oral and intraperitoneal administration



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/055309

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/00 A61K31/198 A61K31/519 A61K9/28 A61K9/48 A61K45/06 A61P25/16 A61P25/28 A61P25/22 A61P25/24 A61P25/14 A61P25/06 A61P1/04		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/059471 A1 (COMPTON BRUCE JON [US] ET AL) 27 March 2003 (2003-03-27) paragraphs [0015], [0041] - [0042], [0074], [0268]; claims 1, 12, 23-27, 29-34, paragraphs [0012] - [0013], [0034]	1-4, 10-14
X	WO 2008/015269 A1 (MERZ PHARMA GMBH & CO KGAA [DE]; DANYSZ WOJCIECH [DE]; DEKUNDY ANDRZEJ) 7 February 2008 (2008-02-07) cited in the application abstract; claims 1-31 formulation example 2 Formulations example 1, 3 ----- -/-	1-15
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 7 May 2012		Date of mailing of the international search report 20/07/2012
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Madalinska, K

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2012/055309

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/015271 A1 (MERZ PHARMA GMBH & CO KGAA [DE]; DANYSZ WOJCIECH [DE]; DEKUNDY ANDRZEJ) 7 February 2008 (2008-02-07) cited in the application abstract; claims formulation example 2 formulation example 1,3 -----	1-15
A	JEAN-PHILIPPE ROCHER ET AL: "mGluR5 negative allosteric modulators overview: a medicinal chemistry approach towards a series of novel therapeutic agents.", CURRENT TOPICS IN MEDICINAL CHEMISTRY, vol. 11, no. 6, 1 January 2011 (2011-01-01), pages 680-695, XP055006630, ISSN: 1568-0266 abstract page 680, right-hand column, last paragraph page 681 - page 683; figures 1-14; tables 1-6 -----	1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2012/055309

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

6-9, 12(completely); 1-5, 10, 11, 13-15(partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 6-9, 12(completely); 1-5, 10, 11, 13-15(partially)

Pharmaceutical formulation comprising a pyrazolo[1,5-a]pyrimidines as negative allosteric modulator (NAM) of the mGluR5 receptor, wherein the pharmaceutical formulation release this NAM in the small and/or large intestine

2. claims: 1-5, 10, 11, 13-15(all partially)

Pharmaceutical formulation comprising tetrahydroquinolinones as negative allosteric modulator (NAM) of the mGluR5 receptor, wherein the pharmaceutical formulation release this NAM in the small and/or large intestine

3. claims: 1-5, 10, 11, 13-15(all partially)

Pharmaceutical formulation comprising fused pyridines as negative allosteric modulator (NAM) of the mGluR5 receptor, wherein the pharmaceutical formulation release this NAM in the small and/or large intestine

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/055309

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Information on patent family members

International application No

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