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MERZ PHARMA GMBH & CO. KGAA [DE/DE]; Eckenheimer LandstraBe 100, 60318 Frankfurt am Main (DE).

HAUPTMEIER, Bernhard [DE/DE]; Neue Weinbergstr. 10, 63571 Gelnhausen (DE).

KIEHM, Kevin [DE/DE]; Landgraf-Philipp-Str. 44, 60431 Frankfurt am Main (DE).

PLITT, Patrick [DE/DE]; Homburger Weg 7, 61352 Bad Homburg (DE).

SZLAK-FREIER, Alda [DE/DE]; Woog Str. 36c, 60431 Frankfurt am Main (DE).

Agent: JACOBI, Markus; Isenbruck Bosl Horschler LLP Patentanwalte, EASTSITE ONE, Seckenheimer LandstraBe 4, 68163 Mannheim (DE).


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

PHARMACEUTICAL COMPOSITION COMPRISING A PYRAZOLOPYRIMIDINE AND CYCLODEXTRIN

Pharmaceutical compositions comprising at least a substituted pyrazolo[1,5-a]pyrimidine compound (P) or a pharmaceutically acceptable salt or a stereoisomeric form thereof, and at least one pharmaceutically acceptable cyclodextrin derivative (C), and optionally one or several further components (F), such as a co-solvent, have unexpected stabilities.
Pharmaceutical Composition Comprising a Pyrazolopyrimidine and Cyclodextrin

Field of the Invention

The present invention relates to pharmaceutical compositions containing at least one pyrazolopyrimidine derivative and at least one cyclodextrin. The invention also deals with a process for the preparation of a pharmaceutical composition containing at least one pyrazolopyrimidine derivative and at least one cyclodextrin. The invention also relates to different medical uses of these pharmaceutical compositions.

Background of the invention

Various types of pyrazolopyrimidine derivatives have been described in the literature. For example, different types of substituted pyrazolopyrimidine compounds have been disclosed in WO 2008/015269, WO 2008/015270, WO 2008/015271, WO 2009/095253, WO 2009/095254 and WO2007/006530, wherein the pyrazolo[l,5-a]pyrimidines disclosed are negative modulators of the known receptor mGluR5.

In WO 2004/087153 various 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[l,5-a]pyrimidines for the treatment of diseases is described where it is desirable to inhibit the enzyme 11BHSD1.

In WO 2003/037900, further specific pyrazolopyrimidine compounds are described as inhibitors of ion-channels in human cells. 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 pyrazolopyrimidine derivatives which have a NADPH-oxidase inhibitor activity are described.

US 2010/249138 discloses pyrazolopyrimidines of general formula (GK1) and pharmaceutical compositions for the treatment of syndromes after cessation of compulsive behaviours.
In document US 2010/249138, the preparation of an acidic solution (in HCl) of the following compound with 25% (w/v) hydroxypropyl -P-cyclodextrin is mentioned.

US 2006/0189633 describes the pyrazolopyrimidine derivate drug Indiplon, which contains a polar acetamido-group and is having the following structure.

This compound can be formulated as powder, tablet or oral solution. Various carriers for the compound are described in US 2006/0189633, e.g. selected from the large group of claim 13, encompassing polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), lactose,
starches, mannitol, methylcellulose, hydroxymethylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxylpropylcellulose, hydroxypropylmethylcellulose (HPMC), a-cyclodextrin, β-cyclodextrin and hydroxylpropyl-a-cyclodextrin.

In WO 2011/064237, co-crystals of 6-bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(l-methyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone are described, which can be used for CNS-disorders. The co-crystals can be formulated as pharmaceutical formulations such as tablets, capsules and powder formulations.

In WO 2008/015269, pyrazolo[1,5-a]pyrimidine derivatives are disclosed, which are linked to a heterocyclic amine and which are potent modulators of the receptor mGluR5. Many pyrazolo[1,5-a]pyrimidine derivatives have a low solubility in water, e.g. lower than 0.1 mg per ml of water. Furthermore, the wettability of many pyrazolo[1,5-a]pyrimidine derivatives is very low (measured by contact angles theta > 90°), so that the preparation of aqueous compositions is difficult.

As lipophilic pharmaceutical compounds, the pyrazolo[1,5-a]pyrimidines often exhibit an octanol/water partition coefficient log P greater than 1, in particular from 2 to 5. The lipophilicity of a compound can in general be expressed by the logP or logD value, which is a high value for lipophilic compounds and very low value for hydrophilic compounds. The octanol/water partition coefficient (logP) of the compounds tested according to this invention can be determined by accepted standard methods, such as OECD (1995), Test No. 107: Partition Coefficient (n-octanol/water): Shake Flask Method, OECD Guidelines for the Testing of Chemicals, Section 1: Physical-Chemical properties, OECD Publishing. The logP value may be determined according to the Draft OECD guideline OECD (2000), OECD Draft guideline for the Testing of Chemicals: 122 Partition Coefficient (n-Octanol/Water): pH-Metric Method for Ionisable Substances.

Pharmaceutical compositions containing pyrazolo[1,5-a]pyrimidine derivatives often are difficult to prepare and/or not stable during storage, in particular when formulated as aqueous preparations. Furthermore, for many pharmaceutical applications, the amount of pyrazolo[1,5-a]pyrimidine derivative needed at the specific site of action is higher than conventional pharmaceutical formulations can provide with.
In particular, substituted pyrazolo[1,5-a]pyrimidine derivatives, such as those mentioned in WO 2008/015269, are molecules with a very low aqueous solubility of e.g. only 2 to 50 microgram per milliliter. The solubility in aqueous media can often not be improved by the adjustment of pH-value, as many pyrazolo[1,5-a]pyrimidine derivatives have no relevant basic or acidic groups.

One way of improving solubility is the use of solvents in combination with co-solvents. This strategy is often not favored, as the toxicological impact of these excipients in the requested (high) amounts can be a major disadvantage. Alternative formulations use the lipophilicity of the compounds to dissolve them in oils, fats and waxes to develop "oily solutions" and related formulations like emulsions for oral and parenteral applications. Some disadvantages of these previously described "oily formulations" are their high calorimetric input, their unpleasant mouth-feel and taste and also limitations to increase the solubility of the compounds. Furthermore, the formulation of oil-water-combinations is often difficult.

Solvents (such as water) and co-solvents (such as DMSO or glycerol) can be used in combination to prepare solutions with pyrazolo[1,5-a]pyrimidine compounds. However, only limited amounts of the co-solvents should be used in preclinical and clinical studies. The acceptable amounts are even lower for marketed drug products for acute and chronic applications in humans.

One other way of improving solubility is the use of surfactants to design aqueous based solutions for oral applications. This can also lead to an improvement of the solubility of pyrazolopyrimidines. However, the toxicological acceptance of surfactants in preclinical studies and in human used drug products for acute and chronic use is often limited, the challenges and limitations are similar to those of co-solvent based approaches.

Therefore, the development of liquid, semi-solid and solid formulations, in particular of aqueous based formulations, for various types of substituted pyrazolo[1,5-a]pyrimidines, such as those mentioned in WO 2008/015269, and for different application routes is a challenging task. The compositions should provide with pharmacologically active and well tolerated concentrations of the pyrazolo[1,5-a]-pyrimidine compounds. The low solubility in aqueous media also limits the drug product design space and poses a challenge for preclinical studies and the clinical testing phases and may limit the development options for the marketed drug products.
Detailed Description

As one aspect of the invention, the hydrophobic small molecules of the substituted pyrazolo[1,5-a]pyrimidine derivatives (P) were found to be solubilised by the use of cyclodextrin derivatives (C), e.g. via the formation of van-der-Waals complexes. The pharmaceutical composition of this invention often comprises a pyrazolo[1,5-a]pyrimidine derivative which has a molecular weight between 200 and 800 g/mol, such as those mentioned in WO 2008/015269.

The composition also contains, as an additional component, together with the active compound (P), a cyclodextrin derivative (C). Cyclodextrins (C) are known to be cyclic oligosaccharides with a hydrophilic outer surface and a hydrophobic cavity. Typical examples of cyclodextrins are alpha-cyclodextrins, beta-cyclodextrins and gamma-cyclodextrins. They differ in the size of the cavity formed by the sugar-units. For the purpose of this invention, beta-cyclodextrins and gamma-cyclodextrins are preferably used. In particular, non-native cyclodextrins are used, in particular cyclodextrins that have been chemically modified, e.g. by hydroxyalkylation. These can be used with poorly soluble pyrazolo[1,5-a]pyrimidine derivatives (P), such as those mentioned in WO 2008/015269.

By special manufacturing methods, formulations can be prepared, which increase the solubility of a pyrazolo[1,5-a]pyrimidine derivative into the milligram/ml range. The formation of complexes of a pyrazolo[1,5-a]pyrimidine derivative (P), such as those mentioned in WO 2008/015269, and a cyclodextrin derivative (C) can occur with and without heating and in the absence of further excipients (e.g. co-solvent or emulsifier).

The invention therefore relates to pharmaceutical compositions comprising at least one pyrazolo-[1,5-a]pyrimidine compound (P) or a pharmaceutically acceptable salt (or a co-crystal) or a stereoisomeric form (or a polymorphic form) thereof and at least one pharmaceutically acceptable cyclodextrin compound (C) and optionally one or more further components (F).

The invention also relates to a pharmaceutical composition comprising at least one pyrazolo[1,5-a]pyrimidine compound (P) of formula (I)
wherein:
Y represents N or C-
Y represents N or C-
Y represents N or C-
Y represents N or C-
wherein at least two of the groups Y to Y denote a carbon atom,
(often three or four of the groups Y to Y denote carbon atoms)
R represents chloro or bromo;
R and R each independently represent hydrogen, Ci-alkyl, C-cycloalkyl or trifluoromethyl;
R and R each independently represent hydrogen, Ci-alkyl, C-cycloalkyl or trifluoromethyl;
R and R independently represent hydrogen, Ci-alkyl, C-cycloalkyl or trifluoromethyl;
R and R 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, nitro, cyano, trifluoromethyl, trifluoromethoxy, Ci-alkyl and Ci-alkoxy;
or a pharmaceutically acceptable salt (or a co-crystal) or a stereoisomeric form (or a polymorphic form) thereof, and at least one pharmaceutically acceptable cyclodextrin derivative (C) and optionally one or several further components (F).
The groups Y\textsuperscript{1} to Y\textsuperscript{4} in formula (I) often all denote a carbon atom, in some embodiments of the invention, three or four of the groups Y\textsuperscript{1} to Y\textsuperscript{4} denote carbon atoms.

The invention also relates to a pharmaceutical composition, comprising at least one pyrazolo[1,5-a]pyrimidine compound of formula (I) in which the radicals denote:

\begin{align*}
R^{10} & \text{ and } R^{11} \text{ independently represent hydrogen, halogen, amino, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, } \text{Ci-C}_3 \text{alkyl, } \text{Ci-C}_3 \text{alkyloxy, cyclohexyl, phenyl, or a ring system from the group: thiophene, pyrrole, furane, pyrazole, tetrazole, oxazole, isoxazole, thiazole, pyridine, pyrimidine and morpholino, or a pharmaceutically acceptable salt or a stereoisomeric form thereof. Often, } R^{10} \text{ and } R^{11} \text{ both represent hydrogen.}
\end{align*}

The invention also relates to a pharmaceutical composition comprising at least one pyrazolo[1,5-a]pyrimidine compound of formula (I) in which:

\begin{align*}
R^{2}, & R^{3}, R^{4} \text{ and } R^{5} \text{ independently represent hydrogen, methyl, ethyl or trifluoromethyl; and } R^{6} \text{ and } R^{7} \text{ independently represent hydrogen or methyl, or a pharmaceutically acceptable salt or a stereoisomeric form thereof.}
\end{align*}

The invention also relates to a pharmaceutical composition comprising at least one pyrazolo[1,5-a]pyrimidine compound of formula (I) in which:

\begin{align*}
one \text{ of } R^{2} \text{ and } R^{3} \text{ represents methyl, ethyl or trifluoromethyl and the remaining of } R^{2} \text{ and } R^{3} \text{ represents hydrogen, or a pharmaceutically acceptable salt or a stereoisomeric form thereof.}
\end{align*}

The invention also relates to a pharmaceutical composition comprising a pyrazolo[1,5-a]pyrimidine compound of formula (I) in which:

\begin{align*}
R^{1} \text{ denotes bromo, and one of } R^{2} \text{ and } R^{3} \text{ represents methyl, ethyl or trifluoromethyl and the remaining of } R^{2} \text{ and } R^{3} \text{ represents hydrogen, or a pharmaceutically acceptable salt or a stereoisomeric form thereof.}
\end{align*}

The invention also relates to a pharmaceutical composition comprising at least one pyrazolo[1,5-a]pyrimidine compound of formula (I), wherein:

\begin{align*}
R^{1} \text{ denotes bromo, and } R^{2} \text{ represents methyl or ethyl and } R^{3}, R^{4}, R^{5}, R^{6}, R^{7}, R^{10} \text{ and } R^{11} \text{ all represent hydrogen and which has at least one chiral carbon atom in the R-configuration, or a pharmaceutically acceptable salt or a stereoisomeric form thereof.}
\end{align*}

The chiral carbon atom of the compounds of formula (I) is preferably in the bicyclic amine-part of the amide-molecule, e.g. in the isoquinoline ring system.
The invention also relates to a pharmaceutical composition comprising at least one pyrazolo[1,5-a]pyrimidine compound of formula (I), wherein R^1 denotes bromo, or a pharmaceutically acceptable salt or a stereoisomeric form thereof.

The invention also relates to a pharmaceutical composition comprising at least one pyrazolo[1,5-a]pyrimidine compound of formula (I), which has an octanol/water partition coefficient of log P value greater than 1, in particular from 2 to 5 and often from 2.1 to 4.5.

The invention also relates to a pharmaceutical composition comprising as pyrazolo[1,5-a]pyrimidine compound (P) the following compound of formula (A)

![Pyrazolo[1,5-a]pyrimidine Compound](image)

(A)

or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable cyclodextrin derivative (C) and optionally a further active ingredient (B) and/or one or several further components (F).

The invention also relates to a pharmaceutical composition comprising the compound of formula (A) and a cyclodextrin derivative (C) selected from beta-cyclodextrins and gamma-cyclodextrins. In one embodiment of the invention, the cyclodextrin compound (C) is selected from the group consisting of randomly alkylated beta-cyclodextrins and hydroxyalkyl-substituted beta-cyclodextrins.

The further active ingredients (B) can e.g. be a known drug compound for the treatment of CNS-diseases, such as Alzheimer-drugs marketed. The further components (F) of the composition (F) are e.g. co-solvents, emulsifiers, preservatives and stabilizers, they are described later more in detail.

The invention also relates to a pharmaceutical composition comprising a pyrazolopyrimidine, such as those mentioned in WO 2008/015269, wherein the at least one cyclodextrin compound (C) is selected from the group of cyclodextrin-derivatives.
consisting of:


In one embodiment of the invention, the cyclodextrin compound (C) is selected from the group consisting of beta-cyclodextrins, alkylated beta-cyclodextrins and 2-hydroxypropyl-beta-cyclo-dextrins. In another embodiment of the invention, the cyclodextrin compound (C) is selected from the group consisting of gamma-cyclodextrins, alkylated gamma-cyclodextrins and 2-hydroxypropyl-gamma-cyclo-dextrins. Often, cyclodextrin-derivatives are used which are modified (in view of native cyclodextrins) by introduction of additional hydroxyl-groups. Furthermore, methyl-beta-cyclodextrines, such as Crysmeb (of Roquette Pharma) can advantageously be used.

From the three major types of pharmaceutically acceptable cyclodextrin derivatives (C), alpha-, beta- and gamma-cyclodextrins, comprising 6, 7 and 8 glucopyranose units, the beta- and gamma-cyclodextrins are preferably used, in particular in chemically modified (non-native) forms. Many chemically modified cyclodextrins can be used to increase the water solubility of the pyrazolopyrimidine compounds (P). These modified beta-cyclodextrin-derivatives are of particular interest for the compositions according to the invention. The term "cyclodextrin-derivatives" includes such modified versions of the native cyclodextrins. A typical example of a suitable grade of hydroxyalkyl-beta-cyclodextrin is amorphous, often randomly substituted hydroxypropyl-beta-cyclodextrin, such as Kleptose. This hydroxyalkyl-beta-cyclodextrin derivative often has a "Degree of Substitution" (DS) in the range of about 4.5, i.e. between approx. 4 and 5, such as the product marketed as Kleptose HPB (by Roquette). It is noted that the DS value, as used herein, defines the average number of substituted hydroxyl groups per anhydro-glucose unit, not per cyclodextrin molecule.
Other examples of useful grades are (e.g. randomly substituted) hydroxypropyl-beta-cyclodextrin with a degree of substitution (DS) in the range of about 5.6, or in the range of 2 to 4, or in the range of 5, or in the range of 6.5, respectively. An example of a suitable grade of hydroxypropyl-gamma-cyclodextrin is the product marketed as Cavasol W8 HP (by Wacker Chemie, Germany).

The invention also relates to a pharmaceutical composition wherein the molar ratio of the pyrazolo[1,5-a]pyrimidine compound (P), such as those of formula (I), and the cyclodextrin derivative (C) is in the range from 1:20 to 1:0.5; in particular from 1:10 to 1:1; often from 1:10 to 1:1.8.

The invention also relates to a pharmaceutical composition wherein the composition is a liquid composition, a semi-solid composition or a solid composition, comprising (in the dosage form) an amount of the pyrazolo[1,5-a]pyrimidine compound (P) in the range from 0.1 to 1000 mg, preferably from 1 to 500 mg, often from 10 to 250 mg.

The invention also relates to a pharmaceutical composition wherein the composition is an aqueous liquid composition, comprising at least 70 % by weight of water and a concentration of the pyrazolo[1,5-a]pyrimidine compound (P) in the range from 1 to 50 mg/ml. The composition also comprises a cyclodextrin derivative (C) (e.g. in the range from 10 to 500 mg/ml) and may comprise as further component (F) one or several co-solvents, in particular one co-solvent. Typical co-solvents are dimethyl sulfoxide (DMSO), 1,3-dimethyl-2-imidazolinone (DMI), dimethyl acetamide (DMA), pyrrolidone (Soluphor P), ethanol, glycerol, PEG 200, PEG 300, PEG 400, propylene glycol and N-methyl-2-pyrrolidone (NMP). For some purposes, other alcohols can be used. The co-solvent often is used in an amount of less than 2 percent by weight, in particular less than 1 percent by weight of the total pharmaceutical composition.

The invention also relates to a pharmaceutical composition, wherein the composition is an aqueous liquid composition, comprising at least 75 % by weight of water and a concentration of the pyrazolo[1,5-a]pyrimidine compound (A) in the range from 1 to 20 mg/ml, and which comprises as one further component (F) a co-solvent from the group of DMSO, DMI, DMA, Soluphor P, ethanol glycerol, PEG 200, PEG 300, PEG 400, propylene glycol and NMP.

The invention also relates to a pharmaceutical composition as described above for the treatment of a disorder or a disease of the central nervous system, in particular of those CNS-diseases described below.
A further aspect of the invention deals with a process for preparation of a pharmaceutical composition as described above, comprising the steps of mixing together at least one pyrazolo[1,5-a]pyrimidine compound (P) or a pharmaceutically acceptable salt or a stereoisomeric form (or a polymorphic form) thereof, and at least one pharmaceutically acceptable cyclodextrin derivative (C) and optionally one or several further components (F). This mixing can be done in a liquid, such as water, at room temperature or at elevated temperature (e.g. 21 to 70°C). For the mixing process the use of high energy mixers can be advantageous. This mixing together can be done without water being present, at room temperature or at elevated temperature (e.g. 21 to 70°C). It is possible to use a co-solvent during this mixing process to facilitate the process.

It was observed that different types of cyclodextrins improve the solubility of pyrazolo[1,5-a]-pyrimidine derivatives with pronounced differences. The complexes can be formed by using different molar ratios of pyrazolo[1,5-a]pyrimidine derivative (P) and cyclodextrin derivative (C). The complexes formed often show a molar ratio of about 1:1 to 10:1, but often the molar amount of cyclodextrin derivative (C) used in the formulation is higher than the molar amount of pyrazolo[1,5-a]pyrimidine derivative (P). In particular the use of hydroxypropyl-beta-cyclodextrin (HPBCD) was found very effective for component (C).

The quantification of the molar ratios in the complexes formed between the pyrazolo[1,5-a]pyrimidine derivative (P), such as compound (A), and the cyclodextrin derivative (C), such as beta cyclodextrin, can be measured by proton nuclear magnetic resonance (in mixtures of D$_2$O and d$_6$-DMSO; with 500 or 800 MHz spectrometer). It is possible to measure the ratios e.g. by integration of the known proton NMR-signals of the pyrazolopyrimidine (e.g. the three protons of the methyl group of Compound (A) or the two H4/6-protons of Compound (A)) and specific protons of the cyclodextrin (the anomeric protons (HI) of the cyclodextrin ring system (C)). Typical complexes of beta cyclodextrin (C) and compound (A) were prepared from molar ratios from 4:1 to 10:1, with no free signals from compound (A) found.

Typical complexes of hydroxypropyl-beta cyclodextrin (HPBCD) and compound (A) were prepared from molar ratios from 1:1 to 10:1, in particular ratios from 5:1 to 10:1. Two different conformations were found for compound (A) in solution, which both form complexes with HPBCD. The aromatic part of compound (A) seems to dock with the narrow end of the HPBCD-molecules.
By integration of the NMR-signals, the molar ratios between the cyclodextrins and compound (A) are in general between 4:1 and 10:1.

For the treatment of disorders and conditions of the central nervous system (CNS), various heterocyclic drug compounds have been developed in recent years, however many diseases, like Alzheimers or Parkinson cannot be treated adequately at low cost because of complex chemical structures, low solubilities of e.g. pyrazolopyrimidines, limited tolerability and minimal efficacy of other the heterocyclic compounds.

It is known in the prior art that cyclodextrins can be used in pharmaceutical compositions. One technical problem is that cyclodextrin-containing formulations are difficult to be combined with standard excipients (such as classical preservatives), since the excipients are often bound and complexed by the cyclodextrin. Thus, for example a preservative may be inactivated by the use of cyclodextrins. Typical uses of cyclodextrins are mentioned e.g. in US 4,596,795, describing a tablet containing progesterone and a cyclodextrin. In WO 2009/156160 the CNS-compound neramexane is mentioned with a cyclodextrin-derivative. In US 5,043,328 some indole derivatives are disclosed, which can be used in combination with fatty acids for pharmaceutical compositions, which also can contain stabilizers such as phospholipids, sugar lipids, proteins or cyclodextrins.

In WO 2009/125246, compositions for treatment of ophthalmic hypertension are described which contain a bicyclic active ingredient, such as dorzolamid, which can be formulated in aqueous solutions together with a cyclodextrin.

One further goal of the present invention is to provide new pharmaceutical compositions which can easily be prepared, based on low-cost active ingredients, which compositions are easily applicable to humans and animals, and are well tolerated and have an acceptable long-term stability (in particular for several months). The compositions described above can be e.g. in the form of a solid composition (e.g. powder, tablet), a semi-solid composition (e.g. gel) or a liquid composition (e.g. solution, suspension). Surprisingly, it was found that the solubility of pyrazolopyrimidine derivatives of formula (I) can be considerably be improved by the use of cyclodextrin derivatives (C). Stable (aqueous) solutions of the pyrazolo[1,5-a]pyrimidine derivatives (P) can be provided.

The invention also relates to a pharmaceutical composition, wherein the molar ratio of the pyrazolo[1,5-a]pyrimidine compound (P), in particular compound (A), and the beta cyclodextrin (BCD) or hydroxypropyl-beta-cyclodextrin (HPBCD) or gamma cyclodextrin...
(GCD) or hydroxypropyl-gamma-cyclodexrin (HPGCD) is in the range from 1:20 to
1:0.5; in particular from 1:10 to 1:1, often from 1:10 to 1:4.

One aspect of the invention relates to a pharmaceutical composition, wherein the
composition is an aqueous liquid composition comprising at least 70 % by weight of water
and wherein the concentration of the compound of formula (I), in particular of formula (A),
is in the range from 1 mg/ml to 50 mg/ml.

In particular, the invention also relates to a pharmaceutical composition comprising a beta
cyclodextrine compound, for example in a concentration of at least 10 mg/ml, for example
from 10 to 500 mg/ml, such as from 50 to 180 mg/ml.

The invention also relates to a pharmaceutical composition comprising a hydrophobic
(lipophilic) pyrazolopyrimidine compound (P). The hydrophilicity and hydrophobicity can
be determined by the octanol/water partition coefficient (logP), for example according to
the standard methods mentioned herein. Generally, a compound having an octanol/water
partition coefficient of logP<1 will be considered hydrophilic. A compound having an
octanol/water partition coefficient of logP>1 will be considered hydrophobic.

The pharmaceutical composition can as further component (F) also contain a pH-regulator,
e.g. to improve the stability. Typical examples are selected from the group consisting of
physiologically acceptable acids, bases (such as NaOH), and acidic and alkaline salts.

The invention also relates to a pharmaceutical composition, such as an aqueous
composition, comprising as further component (F) a co-solvent, and/or an emulsifier
and/or a preservative. Frequently used examples of co-solvents are DMSO and glycerol.
Such water-miscible, organic co-solvents may be incorporated (in small amounts) in order
to solubilise the poorly water-soluble, lipophilic pyrazolopyrimidine compound (P). The
term liquid composition or formulation includes liquid solutions and dispersions, such as
emulsions and suspensions.

The invention also relates in general to a composition comprising as component (F) a
preservative, e.g. in a concentration from 0.1 to 0.0001 % by weight, for example from
0.01 to 0.001 % by weight (of the total formulation). The invention also relates to a
pharmaceutical composition as described above for the treatment of a disorder or a disease
of the central nervous system, such as the following diseases:
Alzheimer's disease, Creutzfeld-Jakob's syndrome/disease, bovine spongiform encephalopathy (BSE), diseases involving β-amyloid and/or tauopathy, motor neuron diseases, amyotrophic lateral sclerosis (ALS), olivopontocerebellar atrophy, post-operative cognitive deficit (POCD), systemic lupus erythematosus, systemic sclerosis, Sjogren's syndrome, Neuronal Ceroid Lipofuscinosis, neurodegenerative cerebellar ataxias, Parkinson's disease, Parkinson's dementia, cognitive impairment, cognitive deficits in various forms of mild cognitive impairment, cognitive deficits in various forms of dementia, dementia pugilistica, vascular and frontal lobe dementia, cognitive impairment, learning impairment, eye injuries, eye diseases, eye disorders, glaucoma, retinopathy, macular degeneration, head or brain or spinal cord injuries, head or brain or spinal cord trauma, trauma, hypoglycaemia, hypoxia, perinatal hypoxia, ischaemia, convulsions, epileptic convulsions, epilepsy, temporal lobe epilepsy, myoclonic epilepsy, inner ear insult, tinnitus, dyskinesias, L-dopa-induced dyskinesias, chorea, Huntington's chorea, athetosis, dystonia, stereotypy, ballism, tardive dyskinesias, tic disorder, torticollis spasmodicus, blepharospasm, focal and generalized dystonia, nystagmus, hereditary cerebellar ataxias, corticobasal degeneration, tremor, essential tremor, abuse, addiction, nicotine addiction, nicotine abuse, alcohol addiction, alcohol abuse, opiate addiction, opiate abuse, cocaine addiction, cocaine abuse, amphetamine addiction, amphetamine abuse, anxiety disorders, panic disorders, anxiety and panic disorders, social anxiety disorder (SAD), attention deficit hyperactivity disorder (ADHD), attention deficit syndrome (ADS), restless leg syndrome (RLS), hyperactivity in children, autism, dementia, dementia in Alzheimer's disease, dementia in Korsakoff syndrome, Korsakoff syndrome, vascular dementia, major depressive disorder, depression, bipolar manic-depressive disorder, irritable bowel syndrome (IBS), migraine, multiple sclerosis (MS), muscle spasms, pain, chronic pain, acute pain, inflammatory pain, schizophrenia, spasticity, Tourette's syndrome, sleep disorders, anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, social phobia, phobic disorders and schizophreniform disorder.

In particular, Parkinson's disease and dyskinesias, such as L-dopa-induced dyskinesias, can be treated by the composition comprising a compound (P) and a cyclodextrin derivative (C).

The invention also relates to a process for preparation of a pharmaceutical composition comprising the steps of mixing together at least one pharmaceutically acceptable compound of formula (I) and at least one pharmaceutically acceptable cyclodextrin derivative (C) and if necessary further pharmaceutically acceptable components (F).
The invention also relates to the use of a cyclodextrin compound (C), in particular of a beta-cyclodextrin, for the preparation of a pharmaceutical composition comprising a pyrazolopyrimidine compound (P) for the treatment of a disease, in particular a CNS-disease. The invention further relates to such a use, wherein the composition is an aqueous liquid composition comprising as further component (F) a co-solvent and/or a preservative.

The invention also relates to such a use wherein the concentration of the cyclodextrin-compound (C) is at least 10 mg/ml, for example 10 to 500 mg/ml, often from 20 to 180 mg/ml.

The compounds of the invention are usually named according to the IUPAC or CAS nomenclature system. Abbreviations which are well known to one of ordinary skill in the art may be used (e.g. "Ph" for phenyl, "Me" for methyl, "Et" for ethyl, "h" for hour or hours, and "rt" for room temperature). The term "analog" or "derivative" is used herein in the conventional pharmaceutical sense referring to a molecule that structurally resembles a reference molecule, but has been modified in a controlled manner to replace one or more specific substituent(s) of the molecule with an alternate substituent, thereby generating a molecule which is structurally similar to the reference molecule.

The composition according to the invention may comprise the compound of formula (I) and/or a "pharmaceutically acceptable salt" and/or a "derivative" and/or a "polymorphic form" and/or one or several "stereoisomeric forms" of a compound of formula (I).

The term "pharmaceutically acceptable" refers to ingredients of the compositions that are physiologically tolerable and do not typically produce untoward reactions when administered to a mammal (such as a human). Preferably, as used herein, the term "pharmaceutically acceptable" means approved by a European or US-regulatory agency or listed in a recognized pharmacopeia for use in mammals.

The compounds of the present invention may be in the form of pharmaceutically acceptable salts, but often they do not form salts. "Pharmaceutically acceptable salts" refers to those salts which possess the biological effectiveness and properties of the parent compound and which are not biologically or otherwise undesirable. The nature of the salt is not critical, provided that it is non-toxic and does not substantially interfere with the desired pharmacological activity. The compounds of the present invention may be in the form of co-crystals with other pharmaceutically acceptable small molecules.
The compounds of the invention having at least one chiral center may exist in and be isolated in optically active (such as R- or S-isomers) and racemic forms. The compounds may exhibit polymorphism. The present invention encompasses any racemic, optically active, polymorphic, tautomeric or stereoisomeric form, or mixture thereof, of a compound of the invention, which possesses the useful properties described herein.

The composition of the invention comprises at least one compound of formula (I) and/or a pharmaceutically acceptable salt thereof and also comprises at least one pharmaceutically acceptable cyclodextrin derivative (C), and optionally one or several further components (F).

The pharmaceutically acceptable salts of the compound (I) can be prepared by known methods. These salts include e.g. acid addition salts, such as salts made with hydrochloric, sulfonic, hydrobromic, hydroiodic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic, pyruvic, malonic, succinic, fumaric, tartaric, citric, benzoic, carbonic, cinnamic, mandelic, methanesulfonic, ethanesulfonic, hydroxylethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclohexane-sulfamic, salicylic, p-aminosalicylic, 2-phenoxybenzoic or 2-acetoxybenzoic acid. Pharmaceutically acceptable salts also include base addition salts, e.g. using cations such as Na, K, Mg, Ca, alkylammonium or choline. All of these salts may be prepared by conventional means. The nature of the salt is not particularly critical, provided that it is non-toxic and does not substantially interfere with the desired pharmacological activity.

The invention in particular relates to aqueous liquid compositions containing a compound (I). These are liquid preparations wherein the major liquid component is water. The compositions normally contain at least 70% by weight, often at least 80% by weight (w/w of the total composition) of water, but these aqueous liquid compositions may further comprise other liquid components, such as one or several pharmaceutically acceptable, organic co-solvents.

The invention also relates to semi-solid compositions. This term means a composition with low viscosity whose major liquid component is water. The semi-solid composition may comprise further components (F), such as pharmaceutically acceptable organic co-solvents, viscosity regulation polymers, pH-regulators, preservatives and emulsifiers. Examples of such further components are ethanol, glycerol, propylene glycol, and polyethylene glycol.
Such water-miscible organic solvents (such as glycerol) may be incorporated for example in order to solubilise an insufficiently water-soluble ingredient, such as the pyrazolopyrimidine. The term semi-solid composition includes in particular gels, but also creams and ointments. In comparison to a liquid composition these formulations have an increased viscosity, compared to aqueous solutions. The viscosity of semi-solid compositions can be controlled by using one or several polymeric components or a combination of polymers.

The term "polymorphic form" of a compound of formula (I) means a particular crystalline or non-crystalline form of a particular compound (I) which has particular physical properties (such as particular X-ray structure) with differ from the properties of a compound having the same chemical formula.

The term "stereoisomeric form" of compound (I) is used herein in the conventional chemical sense to refer to a molecule that has the same summarizing chemical formula but differs in the structure. Typical examples are enantiomers, diastereoisomers and racemates. The term "heteroaryl" means an aromatic heterocyclic system, in particular having 5 or 6 membered ring systems, which contain at least one atom which is not a carbon atom, such as e.g. N, S, O. Typical examples are pyridine, pyrimidine, thiophene, etc. The term "heterocycl" means a non-aromatic heterocyclic system, in particular having 5 or 6 membered ring systems, which contain at least one atom which is not a carbon atom, such as e.g. N, S, O. Typical examples are piperidine, pyrrolidine, etc.

The formation of complexes of the pyrazolopyrimidine compounds (P) and the cyclodextrins (C) takes e.g. place in solution and typically is an equilibrium process. Complexes may also occur in solid state. An inclusion complex is a structure wherein a guest molecule is either partially or completely contained within a cavity of a larger host molecule. E.g. the compound (A) can be included in one or several molecules of the cyclodextrin derivative.

The amount of the compound of formula (I) in the pharmaceutical composition may be decided taking into account the desired pharmaceutical use (e.g. for oral or parenteral CNS-formulations), the type of the active ingredient of formula (I) and the concentrations of the other ingredients. The concentration of the active ingredient of formula (I) may be e.g. at least 0.5 mg/ml. If the active ingredient is a compound of formula (I), the concentration in a (liquid) formulation often is in the range from 0.1 to 100 mg/ml, for example 1 to 50 mg/ml, and often from 1 to 30 mg/ml.
The amount of cyclodextrin-derivative (C) in the composition may be selected taking into account the type of cyclodextrin (C) and the concentration of the active compound (I) and the pharmaceutical use. The concentration of the cyclodextrin-derivative (C) in the composition often is at least 5 mg/ml, for example 10 to 250 mg/ml.

For example, a concentration of 0.1 to 100 mg/ml of a compound of formula (I), or a pharmaceutically acceptable salt thereof, may be formulated in such a composition. According to the present invention, for example liquid or semi solid compositions may be prepared with a molar ratio of a compound of formula (I) to cyclodextrin-derivative (C) of from 1 : 20 to 1 : 0.5.

Another embodiment of the invention may comprise a molar ratio of a compound of formula (I) to cyclodextrin-derivative (C) of from 1 : 10 to 1 : 1. It was found that such molar ratios may lead to a remarkably degree of taste masking, which may be associated with the spontaneous formation of a soluble complex between the cyclodextrin molecule and the drug of formula (I). After oral or topical (e.g. into the eye) administration, the compound of formula (I) is rapidly absorbed from the composition and becomes bioavailable.

The composition of the invention may further comprise, besides the pyrazolopyrimidine compound (P) at least one further active ingredient (B), such as a further drug compound useful for the treatment of CNS-diseases. Typical examples are the commercial products for treatment of Alzheimer's and Parkinson disease.

As further components (F) which improve the character of the pharmaceutical composition, for oral compositions, one or more sweeteners may be incorporated into the composition. Furthermore, one or more flavours, flavour enhancers, and taste masking agents may be used. Typical sweeteners are natural or synthetic compounds which have a sweet taste and are physiologically acceptable. Examples of natural sweeteners include common sugars and sugar alcohols such as sucrose, glucose, fructose, maltose, maltitol, xylitol, lactitol, mannitol, and sorbitol. A sugar alcohol may be used to improve the flavor of the composition of the invention, for example sorbitol. A useful concentration range for sorbitol or other sugars and sugar alcohols is from about 5 % (w/v) to about 25 % (w/v). Useful artificial sweeteners include saccharin-sodium, Saccharin, sodium cyclamate, acesulfame K, neohesperidine dihydrochalcone, and aspartame, as well as any other sweeteners whose safety in human use is established.
Appropriate concentrations depend on the individual sweetener which is selected, but also on the specific cyclodextrin which is chosen. For example, hydroxypropyl-beta-cyclodextrin already provides for a rather sweet taste, so that the addition of a sweetening agent may not increase the palatability of the formulation any further. Suitable flavors which may further improve the taste of cyclodextrin-containing aqueous compositions of compounds of formula (I) (including compound (A) and pharmaceutically acceptable salts thereof) include grape, orange, peppermint, spearmint, cherry, liquorice, and aniseed. In particular, peppermint flavours are physicochemically and organoleptically well-compatible with the key components of the composition of the invention and may lead to palatable formulations.

For liquid compositions, the preservation of the active compound of formula (I) can be important. It is possible to formulate the composition without any additional preservative. In one embodiment, the composition of the invention is substantially free of preservatives. In this context, the term "substantially" means that preservatives are not detectable in the composition, or only in concentrations which are generally considered irrelevant with regard to any preservation effects. The pharmaceutical composition may optionally comprise as further component (F) at least one preservative. Whether a composition is effectively preserved may be determined according to tests known in the art. The pharmaceutical composition can also contain as further component (F) a preservative such as benzalkonium chloride, cetlypyridium chloride, cetrimide, cetyl trimethyl-ammonium bromide, benzethonium chloride, chlorhexidine gluconate, ethanol, isopropanol, propylen glycol, butylparaben, ethylparaben, methylparaben, propylparaben, sorbic acid, benzoic acid, thiomersal, organomercury components, chlorobutanol and/or benzyl alcohol.

The preparation of the composition comprising the pyrazolopyrimidine (P) according to the invention is technically easy, quick and cost-efficient. For the preparation of the compositions, the components are e. g. weighed and the compound of formula (I) is combined (mixed) with measured amounts of the cyclodextrin-derivative (C) and water and optionally further components (F), optionally followed by stirring until dissolution occurs. The mixture may be agitated, sonicated and/or heated for some time, e. g. from 2 minutes to 64 hours. The solution may be further processed by filtration or centrifugation to remove residual particles. If a solid formulation is desired, the solution may be dried, such as by tray drying, spray drying or freeze drying.

As pyrazolo[1,5-a]pyrimidin compounds (P) the following compounds are mentioned with the following chemical names:
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-hydroxy-7-methoxy-1-methyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-methyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-methyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3,3-dimethyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3,3-dimethyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dimethoxy-1-methyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dimethoxy-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dimethoxy-1-methyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dimethoxy-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dimethoxy-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-hydroxy-7-methoxy-1-methyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-hydroxy-7-methoxy-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-hydroxy-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dimethoxy-3-methyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dimethoxy-3-methyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dimethoxy-3-methyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-methyl-5,8-dihydro-6H-[1,7]naphthyridin-7-yl)-methanone
(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
(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-[2,6]naphthyridin-6-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-3,4-dihydro-1H-[2,6]naphthyridin-6-yl)-methanone
(6-Chloro-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)-(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)-(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
(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
(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
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-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-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-fluoro-1-ethyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-fluoro-1-ethyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-fluoro-1-ethyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-fluoro-1-ethyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-fluoro-1-ethyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-fluoro-1-ethyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-fluoro-1-ethyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-fluoro-1-trifluoromethyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-fluoro-1-trifluoromethyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-fluoro-1-trifluoromethyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-fluoro-1-trifluoromethyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone

(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-fluoro-1-trifluoromethyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-fluoro-1-trifluoromethyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-fluoro-1-trifluoromethyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-fluoro-1-trifluoromethyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone

(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3-ethyl-1-methyl-3,4-dihydro-lH-isoquinolin-2-yl)methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-((R)-3-methyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-((S)-3-methyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(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
(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
(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
(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
(6-Bromopyrazolo[1,5-a]pyrimidin-2-yl)-(1-ethyl-3,4-dihydro-1H-isoquinolin-2-yl)methanone
(6-Bromopyrazolo[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-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-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-trifluoromethyl-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
(6-Choro-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
(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
(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;
(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
(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
(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
(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
(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
(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
2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-7-carbonitrile
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-pyridin-3-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)-(1-methyl-7-pyrimidin-5-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
(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)-(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)-(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
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-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
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(l-methyl-6-pyrimidin-5-yl-3,4-dihydro-1H-isoquino
lin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(l-methyl-5-pyrimidin-5-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(l-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
(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
(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-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,5-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
(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
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
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
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
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
(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
(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)-(6-pyridin-4-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-methyl-8,9-dihydro-6H-[1,3]dioxolo[4,5-f]isoquinolin-7-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
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-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-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyridin-2-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyridin-2-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyridin-2-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyridin-2-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyridin-2-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-pyridin-2-yl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
(5-Bromo-3,4-dihydro-IH-isoquinolin-2-yl)-(6-bromo-pyrazolo[1,5-a]pyrimidin-yl)-methanone
(5-Bromo-3,4-dihydro-IH-isoquinolin-2-yl)-(6-chloro-pyrazolo[1,5-a]pyrimidin-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-pyridin-2-yl-3,4-dihydro-IH-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-(2,4-dimethoxy-pyrimidin-5-yl)-l-methyl-3,4-dihydro-IH-isoquinolin-2-yl]-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-(2,4-dimethoxy-pyrimidin-5-yl)-l-methyl-3,4-dihydro-IH-isoquinolin-2-yl]-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-(2,6-dimethoxy-pyridin-3-yl)-l-methyl-3,4-dihydro-IH-isoquinolin-2-yl]-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-(2,6-dimethoxy-pyridin-3-yl)-l-methyl-3,4-dihydro-IH-isoquinolin-2-yl]-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-(2-methoxy-pyridin-3-yl)-l-methyl-3,4-dihydro-IH-isoquinolin-2-yl]-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-(2-methoxy-pyridin-3-yl)-l-methyl-3,4-dihydro-IH-isoquinolin-2-yl]-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-(6-fluoro-pyridin-3-yl)-l-methyl-3,4-dihydro-IH-isoquinolin-2-yl]-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-(6-fluoro-pyridin-3-yl)-l-methyl-3,4-dihydro-IH-isoquinolin-2-yl]-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-(2-methoxy-pyridin-3-yl)-l-methyl-3,4-dihydro-IH-isoquinolin-2-yl]-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-(2-methoxy-pyridin-3-yl)-l-methyl-3,4-dihydro-IH-isoquinolin-2-yl]-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-(2-fluoro-pyridin-3-yl)-l-methyl-3,4-dihydro-IH-isoquinolin-2-yl]-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-(2-fluoro-pyridin-3-yl)-l-methyl-3,4-dihydro-IH-isoquinolin-2-yl]-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-(6-fluoro-pyridin-3-yl)-l-methyl-3,4-dihydro-IH-isoquinolin-2-yl]-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-(6-fluoro-pyridin-3-yl)-l-methyl-3,4-dihydro-IH-isoquinolin-2-yl]-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-(6-fluoro-pyridin-3-yl)-l-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-(2,6-dimethoxy-pyridin-3-yl)-l-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)-l-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)-l-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)-l-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-(2-fluoro-pyridin-3-yl)-l-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-(2-fluoro-pyridin-3-yl)-l-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-(2-fluoro-pyridin-3-yl)-l-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-(2-fluoro-pyridin-3-yl)-l-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(l-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
(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-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-furan-3-yl-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6-furan-3-yl-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-furan-3-yl-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone
(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-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
(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
(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
(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-5-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydro-1H-isooquinolin-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-isooquinolin-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-isooquinolin-2-yl]-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-6-(3-methyl-1H-pyrazol-4-yl)-3,4-dihydro-1H-isooquinolin-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-isooquinolin-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
(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-8-(2H-tetrazol-5-yl)-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
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-6-nitro-3,4-dihydro-1H-[2,7]naphthyridin-2-yl]-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-7-nitro-3,4-dihydro-1H-[2,7]naphthyridin-2-yl]-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-8-nitro-3,4-dihydro-1H-[2,7]naphthyridin-2-yl]-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-6-(2H-tetrazol-5-yl)-3,4-dihydro-1H-[2,6]naphthyridin-2-yl]-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-5-(2H-tetrazol-5-yl)-3,4-dihydro-1H-[2,6]naphthyridin-2-yl]-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-5-(5-methyl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)]-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-[1-methyl-8-(5-methyl-7,8-dihydro-6H-pyrido[3,4-d]pyrimidin-7-yl)]-methanone
(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
(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-tetrahydroisoquinoline-5-carbonitrile
2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline-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-[3,7]phenanthroline-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
(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-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]phenanthroline-3-yl)-methanone
1-[2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline-5-yl]-ethanone
2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid methyl ester
2-(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline-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
(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-tetrahydropyrrolo[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
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-lH-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(5-diethylamino-1-methyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(8-diethylamino-1-methyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(7-diethylamino-1-methyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-difluoro-1-methyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-difluoro-1-methyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dichloro-1-methyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dichloro-1-methyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dibromo-1-methyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(6,7-dibromo-1-methyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-morpholin-4-yl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-7-morpholin-4-yl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-8-morpholin-4-yl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-8-morpholin-4-yl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(1-methyl-6-morpholin-4-yl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(l-methyl-6-morpholin-4-yl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(l-methyl-5-morpholin-4-yl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(l-methyl-5-morpholin-4-yl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(l-methyl-7-piperidin-1-yl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(l-methyl-7-piperidin-1-yl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(l-methyl-7-pyrrolidin-1-yl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone
(6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-(l-methyl-7-pyrrolidin-1-yl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone.

The invention is further illustrated by the following examples and the patent claims.

**Example 1** Cyclodextrin-complexes of pyrazolopyrimidines

Different pharmaceutical compositions were prepared by using as pyrazolopyrimidine-component (P) the compound (A), which is of particular interest and has the chemical name:

(6-Bromo-pyrazolo[1,5-a]pyrimidine-2-yl)-(l (R)-methyl-3,4-dihydro-lH-isoquinoline-2-yl)-methanone.

This compound (A) is the R-enantiomer, but both isomers (R and S) were prepared by classical chemical synthesis.

The compound (A) was tested in various compositions (formulations) inter alia for CNS-applications. The compound (A) is a small molecule having a molecular weight of about 360 g/mol, but is very little soluble in aqueous media (about 0.001 to 0.01 mg/ml).

The compound (A) can be formulated as aqueous based, liquid solutions with over 100-fold higher concentrations of the drug substance avoiding the use of larger amounts of excipients, such as co-solvents.
These pharmaceutical solutions can be easily applied to different animal species and human beings via nearly all application routes like the oral, buccal, dermal, nasal, rectal, vaginal, pulmonary, ocular and parenteral route. The compound (A) is a lipophilic compound with limited wettability and solubility in aqueous media. The lipophilicity can be expressed by the logP value, which is approximately 3 for compound (A).

The following cyclodextrin derivatives (C) were investigated:

- Gamma-cyclodextrin (designated as GCD or γ-CD), e.g. Cavamax W8

  Crystalline, melting point 267°C

- Hydroxypropyl-gamma-cyclodextrin (see HPGCD or HP-γ-CD), e.g. Cavasol W8HP

  Amorphous, degrades at 250°C

- Beta-cyclodextrin (designated as BCD)

  Crystalline hydrate, melting point 298°C

- Hydroxypropyl-beta-cyclodextrin (designated as HPBCD), e.g. Kleptose HPB.

  Amorphous, degrades at 260°C

- Methylbeta-cyclodextrin (designated as MBCD, experimental type).

The pharmaceutical compositions were prepared by using as cyclodextrin component (C) different amounts of a suitable grade of the above mentioned beta- and gamma-cyclodextrins. HPBCD is e.g. an amorphous, randomly substituted hydroxypropyl-beta-cyclodextrin, having a "Degree of Substitution" (DS) in the range between 4 and 5. In one embodiment, the commercial product Kleptose HPB (marketed by Roquette) was used.

An aqueous solution comprising 16 % by weight of hydroxypropyl-beta-cyclodextrin (HPBCD) was prepared. At a temperature of 50° C, 5 mg of compound (A) can be solved in 1 ml of the HPBCD-solution, a stable complex was formed.

**Example 2** Cyclodextrin-complexes of pyrazolopyrimidines without co-solvent

As pyrazolopyrimidine component, (6-Bromo-pyrazolo[1,5-a]-pyrimidine-2-yl)-(l(R)-methyl-3,4-dihydro-lH-isoquinoline-2-yl)-methanone, compound (A) was used, which is very poorly soluble in aqueous media. However it can be formulated as aqueous based, liquid solutions with over 100-fold higher concentrations of the drug substance using low amounts of specific cyclodextrines (HPBCD).
These solutions can be easily applied to different animal species and human beings via nearly all application routes like the oral, dermal, nasal, rectal and parenteral route. The following compositions were prepared by mixing the respective cyclodextrine compound (C) and the Compound (A) with distilled water at 37°C for 64 hours, followed by filtration (PTFE-filter) and then analysis by High Performance Liquid Chromatography (Agilent 1100; Water/Acetonitrile/Perchloric acid):

a) 1 ml water + 450 mg cyclodextrin + 10 mg Compound (A)  
b) 1 ml water + 300 mg cyclodextrin + 10 mg Compound (A)  
c) 1 ml water + 200 mg cyclodextrin + 10 mg Compound (A)  
d) 1 ml water + 100 mg cyclodextrin + 10 mg Compound (A)  
e) 1 ml water + 50 mg cyclodextrin + 10 mg Compound (A)  
f) 1 ml water + 25 mg cyclodextrin + 10 mg Compound (A).

These experiments were performed at pH 7.0 and with buffered water at pH 6.8, pH 7.4 and pH 1.2.

The solubility of Compound (A) without cyclodextrin-derivative (C) was found as follows:

<table>
<thead>
<tr>
<th>pH</th>
<th>Solubility (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>0.006</td>
</tr>
<tr>
<td>6.8</td>
<td>0.004</td>
</tr>
<tr>
<td>7.4</td>
<td>0.002</td>
</tr>
<tr>
<td>1.2</td>
<td>0.006</td>
</tr>
</tbody>
</table>

The compound (A) was found to be considerably solubilised by the use of three types of cyclodextrin derivatives (C). Already at a ratio of 25 mg cyclodextrin + 10 mg Compound (A) per ml water, the formation of van-der-Waals complexes seems to improve solubility of the drug compound.

By using BCD as cyclodextrin, the solubility of Compound (A) in water was increased about 30-times. By using HPGCD as cyclodextrin, the solubility in water was increased about 100-times. By using HPBCD as cyclodextrin, the solubility of Compound (A) in water was increased about 500-times, leading e. g. to the solubility at pH 7 at 20°C of more than 5 mg/ml, which is very useful for oral or parenteral formulations of the drug.
Also by using a methyl-beta-cyclodextrin, the solubility of Compound (A) can be increased. Not only the solubility was increased, but also the time for preparing the solutions can be reduced. The solutions obtained were used for preparing pharmaceutical formulations, e.g. by adding further excipients to the solution and/or by freeze-drying the solutions. The solutions were further used for pharmacological testing.

The products obtained after freeze-drying of the solutions or obtained by crystallization and the pyrazolopyrimidin-CD-complexes formed can be analysed by classical methods, such as X-ray Powder Diffraction, Polarized Light Microscopy, Differential Scanning Calorimetry, IR-Spectroscopy, NMR-Spectroscopy and HPLC. With BCD and GCD, crystallites were obtained and characterized. By NMR-spectroscopy, the complexes formed between compound (A) and different cyclodextrin derivatives can be characterized.

Whereas the three hydrogen of the methyl group (HI 7) of compound (A) have a chemical shift of 1.56 ppm, in the 5:1 complex of HPBCD and compound (A) the signal of the methyl group is found at 1.79 ppm. Similar results were found for the second conformation of compound (A).

**Example 3  Cyclodextrin-complexes of pyrazolopyrimidines with co-solvent**

As drug compound, (6-Bromo-pyrazolo[1,5-a]-pyrimidine-2-yl)-(l(R)-methyl-3,4-dihydro-lH-isoquinoline-2-yl)-methanone, compound (A) was used, which is very poorly soluble in aqueous media. It can be formulated as aqueous based, liquid solution with over 100-fold higher concentrations of the drug substance using small amounts of HPBCD and very low amounts of excipients, such as the co-solvent DMSO.

These solutions can be easily applied to different animal species and human beings via nearly all application routes like the oral, dermal, nasal, rectal and parenteral route.
<table>
<thead>
<tr>
<th>Vehicle</th>
<th>Drug conc. [mg/ml]</th>
<th>Weight of drug [mg]</th>
<th>Preparation, Findings, Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMSO / HPBCD 6% w/w;</td>
<td>≥ 100.3 in pure DMSO</td>
<td>10.3</td>
<td>0.1 ml DMSO were added to Compound (A) and mixed for 2 min. The compound (A) was dissolved. 1 ml of HPBCD was added, the mixture turned milky. After some minutes mixing at 50°C, the mixture became clearer but not transparent. Another 1 ml HPBCD was added and mixed. After 1 hour the mixture was clear by visual inspection.</td>
</tr>
<tr>
<td>The amount corresponds to a molar ratio of 3:1 between HPBCD and COMPOUND (A)</td>
<td>≥ 4.9 in DMSO/HPBCD 6% w/w 5/95 % v/v</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMSO / HPBCD 16% w/w the amount corresponds to a molar ratio of 10 to 1 between HPBCD and COMPOUND (A)</td>
<td>≥ 51 in pure DMSO</td>
<td>5.1</td>
<td>0.1 ml DMSO were added to Compound (A) and mixed for 2 min. The Compound (A) was dissolved. 0.3 ml of HPBCD was added, the mixture turned milky immediately. After some minutes mixing at 50°C, the mixture became clearer but not transparent. Another 0.6 ml HPBCD was added and mixed for 1 minute. The mixture became clear by visual inspection.</td>
</tr>
<tr>
<td>DMSO / HPBCD 20% w/w</td>
<td>≥ 100 in pure DMSO</td>
<td>25</td>
<td>0.25 ml DMSO were added to Compound (A) and mixed for 2 min. The Compound (A) was visually dissolved. 4.75 ml of HPBCD was added, the mixture turned milky immediately. After 1 minute mixing at 50°C the mixture became clearer. It was filtered through 0.2 μm and analysed by HPLC.</td>
</tr>
<tr>
<td></td>
<td>4.47 in DMSO/HPBCD 20% w/w 5/95 % v/v</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMSO / HPBCD 20% w/w</td>
<td>&lt; 500 in pure DMSO</td>
<td>25</td>
<td>0.05 ml DMSO were added to Compound (A) and mixed for 5 min. The Compound (A) was visually not completely dissolved. 4.95 ml of HPBCD was added, the mixture turned milky immediately. After 1 minute mixing at 50°C the mixture became clearer. It was filtered through 0.2 μm and analysed by HPLC.</td>
</tr>
<tr>
<td></td>
<td>4.38 in DMSO/HPBCD 20% w/w 1/99 % v/v</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
This experiment shows that compositions of pyrazolopyrimidines of formula (I) can be easily prepared by using cyclodextrin derivatives (C) in combination to a co-solvent, such as DMSO.

Similar experiments with other co-solvents show that not only the amount of pyrazolopyrimidines of formula (I), in particular compound (A) solved can be increased, but also the time needed for preparing the solutions can be reduced. Also during the process of preparation of pharmaceutical formulations, the application of higher temperatures can be avoided, which is in particular of interest for the specific pyrazolopyrimidines of formula (I), which are sensitive to higher temperatures (e.g. above 50°C) in aqueous media.

**Example 4  Further Cyclodextrin/Pyrazolopyrimidine Formulations**

As pyrazolopyrimidine component, (6-Bromo-pyrazolo[1,5-a]pyrimidin-2-yl)-(3,4-dihydro-1H-isoquinolin-2-yl)-methanone was used, which is very poorly soluble in aqueous media. However it can be formulated as aqueous based, liquid solutions with much higher concentrations of the drug substance using low amounts of specific cyclodextrins, such as hydroxypropyl-beta-cyclodextrins (HPBCD), e.g. Kleptose HPB. Several compositions were prepared by mixing the pyrazolo[1,5-a]pyrimidin compound and the HPBCD with destilled water (and in further experiments with different co-solvents) at 37°C for several hours, followed by filtration (PTFE-filter) and then analysis by High Performance Liquid Chromatography.

The solubility of the pyrazolo[1,5-a]pyrimidin compound without cyclodextrin derivative was very low. By using HPBCD without cosolvent, a strong improvement in solubility can be achieved. The pyrazolo[1,5-a]pyrimidin compound was found to be considerably solubilised (5.2 mg/ml) by the use of 0.3 ml of DMSO in combination with 0.3 ml of PEG400 and 0.4 ml of an aqueous solution of HPBCD (30 % w/w). The solution obtained was stable at room temperature and can be used for preparing pharmaceutical formulations, e.g. by freeze-drying the solutions.
Example 5  Further Cyclodextrin/Pyrazolopyrimidine Formulations

As pyrazolopyrimidine component, 2-[(6-Bromopyrazolo[1,5-a]-pyrimidin-2-yl)carbonyl]-7-methoxy-l-methyl-1,2,3,4-tetrahydro-6-isoquinolin-ol was used, which is poorly soluble in aqueous media. However it can be formulated as aqueous based, liquid solutions with much higher concentrations of the drug substance using low amounts of specific cyclodextrins, such as hydroxypropyl-beta-cyclodextrins (HPBCD), e.g. Kleptose HPB.

Several compositions were prepared by mixing the pyrazolo[1,5-a]pyrimidin compound and the HPBCD with distilled water (and in further experiments with different co-solvents) at 37° C for several hours, followed by filtration (PTFE-filter) and then analysis by High Performance Liquid Chromatography.

The solubility of the pyrazolo[1,5-a]pyrimidin compound without cyclodextrin-derivative was improved using HPBCD without cosolvent. The pyrazolo[1,5-a]pyrimidin compound was found to be considerably solubilised (5.3 mg/ml) by the use of 0.2 ml of DMSO in combination with 0.4 ml of PEG400 and 0.4 ml of an aqueous solution of HPBCD (30 % w/w). The solution obtained was stable and can be used for preparing pharmaceutical formulations, e.g. by freeze-drying the solutions.

Example 6  Further Cyclodextrin/Pyrazolopyrimidine Formulations

As pyrazolopyrimidine component, (6-Chloro-pyrazolo[1,5-a]pyrimidin-2-yl)-((R)-l-methyl-3,4-dihydro-lH-isoquinolin-2-yl)-methanone was used, which is poorly soluble in aqueous media. However it can be formulated as aqueous based, liquid solutions with much higher concentrations of the drug substance using low amounts of specific cyclodextrins, such as hydroxypropyl-beta-cyclodextrins (HPBCD), e.g. Kleptose HPB.

Several compositions were prepared by mixing the pyrazolo[1,5-a]pyrimidin compound and the HPBCD with distilled water (and in further experiments with different co-solvents) at 37° C for several hours, followed by filtration (PTFE-filter) and then analysis by High Performance Liquid Chromatography.

The solubility of the pyrazolo[1,5-a]pyrimidin compound without cyclodextrin-derivative was improved using HPBCD without co-solvent.
The pyrazolo[1,5-a]pyrimidin compound was found to be considerably solubilised (4.8 mg/ml) by the use of 0.2 ml of DMSO in combination with 0.8 ml of an aqueous solution of HPBCD (30 % w/w). The solution obtained was stable at room temperature and can be used for preparing pharmaceutical formulations, e.g. by freeze-drying the solutions.

Corresponding experiments were carried out with 5-Pyridin-3-yl-ethynyl-pyrazolo[1,5-ajpyrimidine.

**Example 7  Cyclodextrin/Pyrazolopyrimidine Formulation without solvent**

The compound (6-Bromo-pyrazolo[1,5-a]-pyrimidine-2-yl)-(l(R)-methyl-3,4-dihydro-lH-isoquinoline-2-yl)-methanone can also be formulated without aqueous media by mixing the compound with the cyclodextrin compound (e.g. HPBCD) as dry composition. The formation of complexes can be observed, even without water being present as solvent. It can be helpful to use small amounts of organic solvents (such as DMSO or alcohols).

With the complex formed, higher concentrations of the drug substance can then be achieved in aqueous pharmaceutical composition, which are stable over several weeks.
Patent Claims

1. Pharmaceutical composition comprising at least one pyrazolo[1,5-a]pyrimidine compound (P) or a pharmaceutically acceptable salt or a stereoisomeric form or a polymorphic form thereof, and at least one pharmaceutically acceptable cyclodextrin derivative (C), and optionally one or several further components (F).

2. Pharmaceutical composition according to claim 1, comprising at least one pyrazolo[1,5-a]pyrimidine compound (P) of formula (I)

\[
\begin{align*}
\text{I} & \\
& \quad \text{wherein,} \\
& Y^1 \text{ represents } \text{N or C-}, \\
& Y^2 \text{ represents } \text{N or C-}, \\
& Y^3 \text{ represents } \text{N or C-}, \\
& Y^4 \text{ represents } \text{N or C-}, \\
& \text{wherein at least two of the groups } Y^1 \text{ to } Y^4 \text{ denote a carbon atom,} \\
& R^1 \text{ represents chloro or bromo;} \\
& R^2 \text{ and } R^3 \text{ each independently represent hydrogen, } \text{C}_3\text{-alkyl,} \\
& \quad \text{C}_3\text{-alkyl} \text{ or trifluoromethyl;} \\
& R^4 \text{ and } R^5 \text{ each independently represent hydrogen, } \text{C}_3\text{-alkyl,} \\
& \quad \text{C}_3\text{-alkyl} \text{ or trifluoromethyl;} \\
& R^6 \text{ and } R^7 \text{ independently represent hydrogen, } \text{C}_3\text{-alkyl,} \\
& \quad \text{C}_3\text{-alkyl} \text{ or trifluoromethyl;} \\
& R^{10} \text{ and } R^{11} \text{ independently represent hydrogen, halogen, amino, hydroxy, nitro,} \\
& \quad \text{cyano, trifluoromethyl, trifluoromethoxy, } \text{C}_3\text{-alkyl, } \text{C}_3\text{-alkyloxy, cyclohexyl,} \\
& \quad \text{phenyl, or a ring system radical from the group: furanyl, thielyn, pyrrolyl, oxazolyl,} \\
& \quad \text{isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiazolyl, thiazoly1, imidazolyl,} \\
& \quad \text{oxadiazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl,} \\
& \quad \text{pyrazolyl, benzofuryl, benzothienyl, indolyl, indolizinyl, isoindolyl, indoliny1,} \\
\end{align*}
\]
indazolyl, benzimidazolyl, benzoazolyl, benzothiazolyl, quinolinyl, quinoxalinyl, quinolizinyl, cinnolinyl, or a pharmaceutically acceptable salt or a stereoisomeric form thereof.

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 can be substituted by one of the following groups: halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, C_i-C_3 alkyl and C_i-C_3 alkoxy; or a pharmaceutically acceptable salt or a stereoisomeric form thereof, and at least one pharmaceutically acceptable cycloextrin derivative (C) and optionally one or several further components (F).

3. Pharmaceutical composition according to claim 1 or 2, comprising at least one pyrazolo[1,5-a]pyrimidine compound of formula (I) in which the radicals denote: R^10 and R^11 independently represent hydrogen, halogen, amino, hydroxy, nitro, cyano, trifluoromethyl, trifluoromethoxy, C_i-C_3 alkyl, C_i-C_3 alkoxy, cyclohexyl, phenyl, or a ring system from the group: thiophene, pyrrole, furane, pyrazole, tetrazole, oxazole, isoxazole, thiazole, pyridine, pyrimidine and morpholino, or a pharmaceutically acceptable salt or a stereoisomeric form thereof.

4. Pharmaceutical composition according to one of the claims 1 to 3, comprising at least one pyrazolo[1,5-a]pyrimidine compound of formula (I) in which R^2, R^3, R^4 and R^5 independently represent hydrogen, methyl, ethyl or trifluoromethyl; and R^6 and R^7 independently represent hydrogen or methyl, or a pharmaceutically acceptable salt or a stereoisomeric form thereof.

5. Pharmaceutical composition according to one of the claims 1 to 4, comprising at least one pyrazolo[1,5-a]pyrimidine compound of formula (I) in which one of R^2 and R^3 represents methyl, ethyl or trifluoromethyl and the remaining of R^2 and R^3 represents hydrogen, or a pharmaceutically acceptable salt or a stereoisomeric form thereof.

6. Pharmaceutical composition according to one of the claims 1 to 5, comprising a pyrazolo[1,5-a]pyrimidine compound of formula (I) in which R^1 denotes bromo, and one of R^2 and R^3 represents methyl, ethyl or trifluoromethyl and the remaining of R^2 and R^3 represents hydrogen, or a pharmaceutically acceptable salt or a stereoisomeric form thereof.
7. Pharmaceutical composition according to one of the claims 1 to 6, comprising at least one pyrazolo[1,5-a]pyrimidine compound of formula (I), wherein R¹ denotes bromo, and R² represents methyl or ethyl and R³, R⁴, R⁵, R⁶, R⁷, R¹⁰ and R¹¹ all represent hydrogen and which has at least one chiral carbon atom in the R-configuration, or a pharmaceutically acceptable salt thereof.

8. Pharmaceutical composition according to one of the claims 1 to 7, comprising at least one pyrazolo[1,5-a]pyrimidine compound of formula (I), wherein R¹ denotes bromo, or a pharmaceutically acceptable salt or a stereoisomeric form thereof.

9. Pharmaceutical composition according to one of the claims 1 to 8, comprising at least one pyrazolo[1,5-a]pyrimidine compound of formula (I), which has an octanol/water partition coefficient of log P value from 2 to 5.

10. Pharmaceutical composition according to any of claim 1 to 9, comprising as pyrazolo[1,5-a]pyrimidine compound (P) the compound of formula (A)

```
    N   N   O
  \   /   /  H
   Br-N-C-N
     \   /  \N
      \ /   |
       \   \R
        \   |
         \  \R
          \  |
           \ |

  (A)
```

or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable cyclodextrin derivative (C) and optionally a further active ingredient (B) and/or one or several further components (F).

11. Pharmaceutical composition according to any of claim 1 to 10, wherein the cyclodextrin derivative (C) is selected from the group consisting of:
12. Pharmaceutical composition according to any of Claims 1 to 11, wherein the compound of formula (I) is of formula (A) and the cyclodextrin derivative (C) is selected from randomly alkylated beta-cyclodextrins and hydroxyalkyl-substituted beta-cyclodextrins.

13. Pharmaceutical composition according to any of claims 1 to 12, wherein the molar ratio of the pyrazolo[1,5-a]pyrimidine compound (P) and the cyclodextrin derivative (C) is in the range from 1:20 to 1:0.5; in particular from 1:10 to 1:1.

14. Pharmaceutical composition according to any of claims 1 to 13, wherein the composition is a liquid composition, a semi-solid composition or a solid composition, comprising an amount of the pyrazolo[1,5-a]pyrimidine compound (P) is in the range from 0.1 to 1000 mg.

15. Pharmaceutical composition according to any of claims 1 to 14, wherein the composition is an aqueous liquid composition, comprising at least 70% by weight of water and a concentration of the pyrazolo[1,5-a]pyrimidine compound (P) in the range from 1 to 50 mg/ml, and which further comprises a cyclodextrin derivative (C) and which may comprise as one further component (F) a co-solvent.

16. Pharmaceutical composition according to any of claims 1 to 15, wherein the composition is an aqueous liquid composition, comprising at least 75% by weight of water and a concentration of the pyrazolo[1,5-a]pyrimidine compound (A) in the range from 1 to 20 mg/ml, and which comprises a cyclodextrin derivative (C) and which comprises as one further component (F) a co-solvent from the group of DMSO, DMI, DMA, Soluphor P, ethanol, glycerol, PEG 200, PEG 300, PEG 400, propylene glycol and NMP.

17. Pharmaceutical composition according to any of claims 1 to 16 for the treatment of a disorder or a disease of the central nervous system.
18. Process for preparation of a pharmaceutical composition according to any of claims 1 to 17 comprising the steps of mixing together at least one pyrazolo[5,1-\ajpyrimidine compound (P) or a pharmaceutically acceptable salt or a stereoisomeric form thereof, and at least one pharmaceutically acceptable cyclodextrin derivative (C) and optionally one or several further components (F).
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

ADD. A61P25/00

According to International Patent Classification (IPC) and/or 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, EMBASE, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELevANT**

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<th>Relevant to claim No.</th>
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Further documents are listed in the continuation of Box C. See patent family annex.

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Date of the actual completion of the international search: 23 January 2013

Date of mailing of the international search report: 31/01/2013

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: Schwal d, Claudi a

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