



(86) Date de dépôt PCT/PCT Filing Date: 2006/09/18
(87) Date publication PCT/PCT Publication Date: 2007/04/12
(85) Entrée phase nationale/National Entry: 2008/03/26
(86) N° demande PCT/PCT Application No.: EP 2006/066446
(87) N° publication PCT/PCT Publication No.: 2007/039439
(30) Priorité/Priority: 2005/09/27 (EP05108910.0)

(51) Cl.Int./Int.Cl. *C07D 471/04* (2006.01),
A61K 31/437 (2006.01), *A61P 25/00* (2006.01),
C07D 487/04 (2006.01)

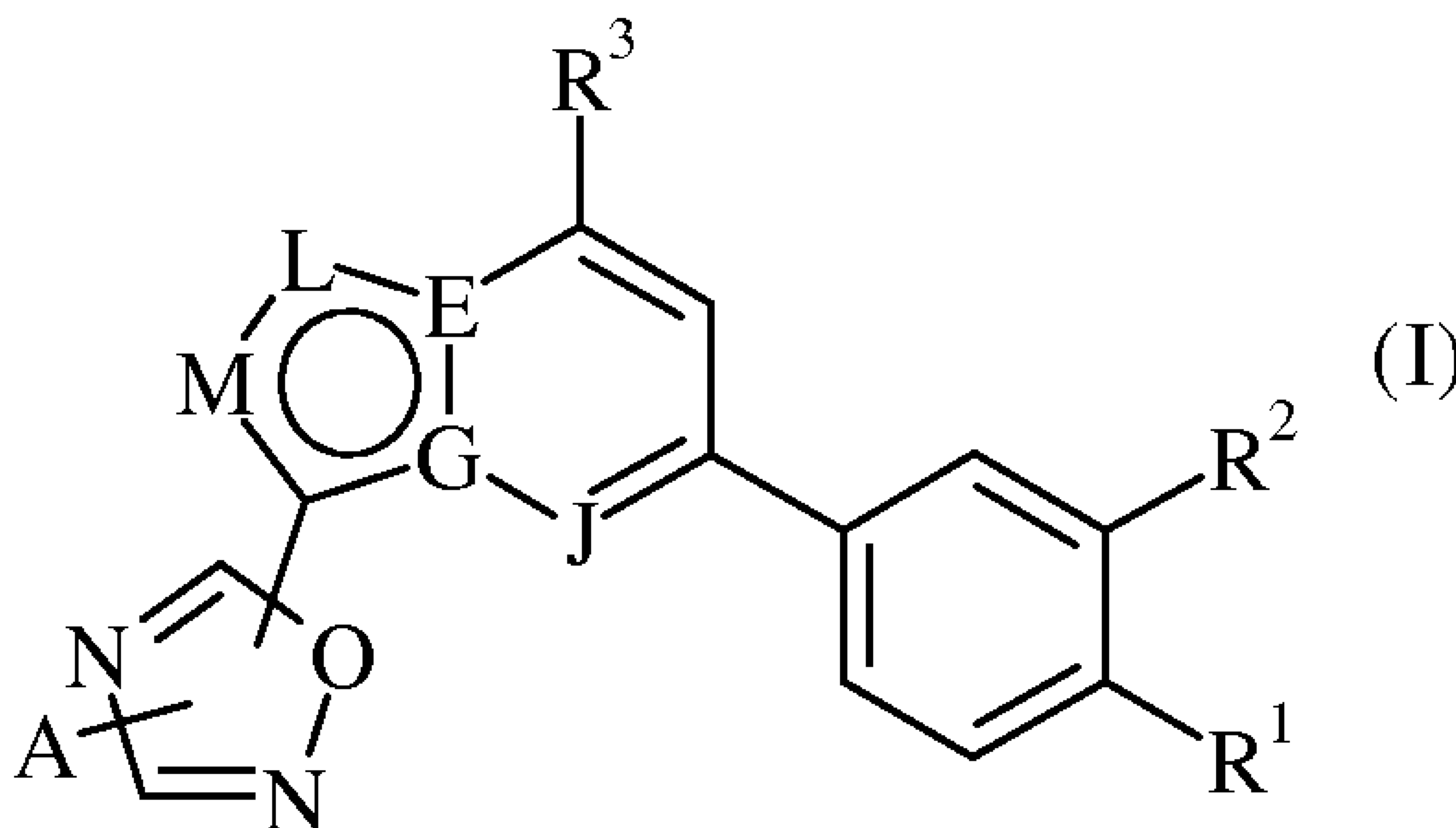
(71) Demandeur/Applicant:
F. HOFFMANN-LA ROCHE AG, CH

(72) Inventeurs/Inventors:
GATTI MCARTHUR, SILVIA, CH;
GOETSCHI, ERWIN, CH;
WICHMANN, JUERGEN, DE;
WOLTERING, THOMAS JOHANNES, DE

(74) Agent: BORDEN LADNER GERVAIS LLP

(54) Titre : OXADIAZOLYL PYRAZOLOPYRIMIDINES EN TANT QU'ANTAGONISTES DE MGLUR2

(54) Title: OXADIAZOLYL PYRAZOLO-PYRIMIDINES AS MGLUR2 ANTAGONISTS



(57) Abrégé/Abstract:

The present invention relates to compounds of formula (I) wherein A, E, G, J, L, R¹, R² and R³ are as defined in the description and claims, a process for the manufacture thereof, their use for the preparation of medicaments for treating CNS disorders and pharmaceutical compositions containing them.



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
12 April 2007 (12.04.2007)

PCT

(10) International Publication Number
WO 2007/039439 A1

(51) International Patent Classification:

C07D 471/04 (2006.01) *A61K 31/437* (2006.01)
C07D 487/04 (2006.01) *A61P 25/00* (2006.01)

(74) Agent: **BRAUN, Axel**; Grenzacherstrasse 124, CH-4070 Basel (CH).

(21) International Application Number:

PCT/EP2006/066446

(22) International Filing Date:

18 September 2006 (18.09.2006)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

05108910.0 27 September 2005 (27.09.2005) EP

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*): **F.HOFFMANN-LA ROCHE AG** [CH/CH]; Grenzacherstrasse 124, CH-4070 Basel (CH).

(72) Inventors; and

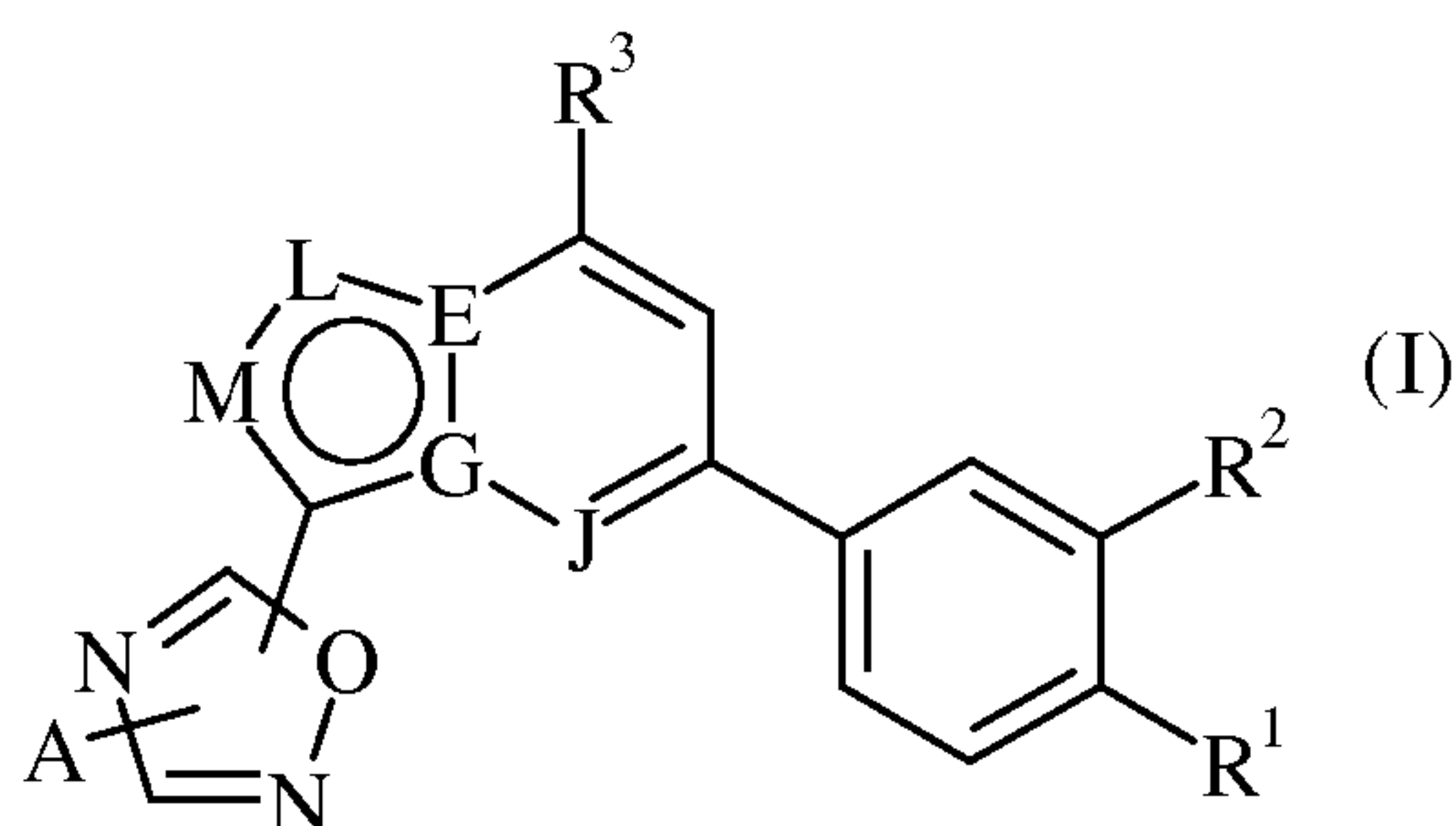
(75) Inventors/Applicants (*for US only*): **GATTI MCARTHUR, Silvia** [IT/CH]; Ramsteinerstrasse 28, CH-4052 Basel (CH). **GOETSCHI, Erwin** [CH/CH]; Landhofweg 23, CH-4153 Reinach Bl (CH). **WICHMANN, Juergen** [DE/DE]; Birkenweg 25, 79585 Steinen (DE). **WOLTERING, Thomas, Johannes** [DE/DE]; In Den Abtsmatten 6, 79639 Grenzach-Wyhlen (DE).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: OXADIAZOLYL PYRAZOLO-PYRIMIDINES AS MGLUR2 ANTAGONISTS



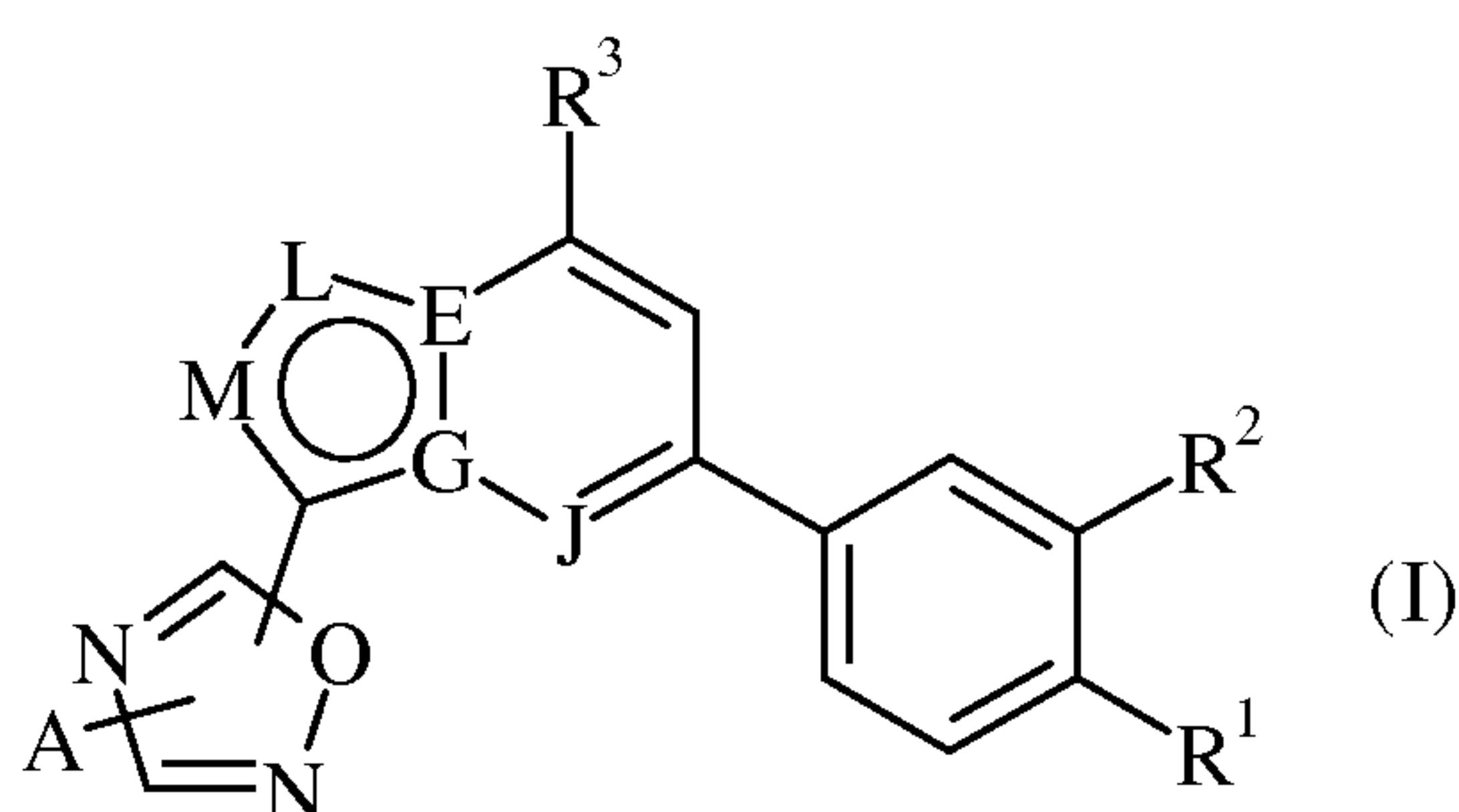
(57) Abstract: The present invention relates to compounds of formula (I) wherein A, E, G, J, L, R¹, R² and R³ are as defined in the description and claims, a process for the manufacture thereof, their use for the preparation of medicaments for treating CNS disorders and pharmaceutical compositions containing them.

WO 2007/039439 A1

OXADIAZOLYL PYRAZOLO-PYRIMIDINES AS MGLUR2 ANTAGONISTS

The present invention relates to compounds of formula (I), a process for the manufacture thereof, their use for the preparation of medicaments for treating CNS disorders and pharmaceutical compositions containing them.

5 In particular, the present invention relates to compounds of general formula (I)



wherein

either E and J are N, G is C and one of L or M is N and the other is CH;

or L and G are N, E is C, and J and M are CH;

10 R¹ and R² are independently from each other H, halogen, C₁₋₆-alkyl optionally substituted by one or more F or by C₁₋₆-alkoxy, C₁₋₆-alkoxy optionally substituted by one or more F;

R³ is H, -C(CH₃)₂OH, linear C₁₋₄-alkyl or C₃₋₄-cycloalkyl which are optionally substituted by one or more substituent(s) selected from the group consisting of 1
15 to 6 F and 1 to 2 OH;

A is selected from the group consisting of aryl or 5 or 6-membered heteroaryl optionally substituted by one to four R^a;

R^a is F, OH, amino, C₁₋₆-alkyl optionally substituted by OH, C₁₋₆-alkoxy, C₃₋₄-cycloalkyl, -CO-R^b, SO₂-R^c or SO₂-NR^dR^e;

20 R^b is amino;

R^c is OH or C₁₋₆-alkyl;

R^d and R^e can be the same or can be different from each others and are selected from the group consisting of:

H;

straight or branched C₁₋₆-alkyl optionally substituted by one or more
substituent(s) selected from the group consisting of F, cyano, OH, di(C₁₋₆-
alkyl)amino, C₃₋₆-cycloalkyl, 5 or 6-membered heterocycloalkyl, aryl or 5 or 6-
membered heteroaryl;
5 C₃₋₆-cycloalkyl;
aryl; or
5 or 6-membered heteroaryl;
or R^d and R^e may, together with the nitrogen atom to which they are attached, form an
heterocyclic ring of 4 to 6 ring members which may be substituted by OH or C₁₋₆-alkyl;
10 as well as pharmaceutically acceptable salts thereof.

It has surprisingly been found that the compounds of general formula I are
metabotropic glutamate receptor antagonists. Compounds of formula I are distinguished
by valuable therapeutic properties.

In the central nervous system (CNS) the transmission of stimuli takes place by the
15 interaction of a neurotransmitter, which is sent out by a neuron, with a neuroreceptor.

L-glutamic acid, the most commonly occurring neurotransmitter in the CNS, plays
a critical role in a large number of physiological processes. The glutamate-dependent
stimulus receptors are divided into two main groups. The first main group forms ligand-
controlled ion channels. The metabotropic glutamate receptors (mGluR) form the second
20 main group and, furthermore, belong to the family of G-protein-coupled receptors.

At present, eight different members of these mGluR are known and of these some
even have sub-types. On the basis of structural parameters, the different influences on the
synthesis of secondary metabolites and the different affinity to low-molecular weight
chemical compounds, these eight receptors can be sub-divided into three sub-groups:
25 mGluR1 and mGluR5 belong to group I, mGluR2 and mGluR3 belong to group II and
mGluR4, mGluR6, mGluR7 and mGluR8 belong to group III.

Ligands of metabotropic glutamate receptors belonging to the group II can be used
for the treatment or prevention of acute and/or chronic neurological disorders such as
psychosis, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits.

30 Other treatable indications in this connection are restricted brain function caused
by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries,
head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia. Further
treatable indications are chronic and acute pain, Huntington's chorea, amyotrophic

lateral sclerosis (ALS), dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficiency functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, opiate addiction, anxiety, vomiting, dyskinesia, 5 depressions, colon cancer, sleep disorders, disorders of circadian rhythms and glioma since mGluR2 antagonists have been found to reduce cell proliferation in human glioma cells (J. Neurochem. March 2003, 84(6): 1288-95).

Objects of the present invention are compounds of formula (I) and their pharmaceutically acceptable salts *per se* and as pharmaceutically active substances, their 10 manufacture, medicaments based on a compound in accordance with the invention and their production, as well as the use of the compounds in accordance with the invention in the control or prevention of illnesses of the aforementioned kind, and, respectively, for the production of corresponding medicaments.

The compounds of formula (I) can also be used in form of their prodrugs. 15 Examples are esters, N-oxides, phosphate esters, glycoamide esters, glyceride conjugates and the like. The prodrugs may add to the value of the present compounds advantages in absorption, pharmacokinetics in distribution and transport to the brain.

Unless otherwise stated, the following terms used in the present description have the definitions given in the following. The term "alkyl" denotes straight-chain or 20 branched saturated hydrocarbon residues with 1 to 6 carbon atoms (C₁₋₆-alkyl), preferably with 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl, i-butyl, t-butyl, as well as those groups which are illustrated with the exemplified compounds of the invention hereinafter.

The term "alkoxy" denotes an alkyl residue in the sense of the foregoing definition 25 bound via an oxygen atom. Examples of "C₁₋₆-alkoxy" residues include methoxy, ethoxy, isopropoxy, as well as those groups which are illustrated with the exemplified compounds of the invention hereinafter. Examples of lower alkoxy substituted by one or more halogen include 2,2,2-trifluoroethoxy groups.

The term "amino" denotes a -NH₂ group.

30 The term "di(C₁₋₆)alkylamino" denotes a -NR⁷R⁸ group, wherein R⁷ and R⁸ are C₁-C₇ alkyl groups as defined herein above. Examples of di(C₁₋₆)alkylamino groups include but are not limited to di(methyl)amino, di(ethyl)amino, methylethylamino, as well as

those groups which are illustrated with the exemplified compounds of the invention hereinafter.

The term "aryl" represents an aromatic carbocyclic group consisting of one individual ring, or one or more fused rings in which at least one ring is aromatic in nature. Preferred aryl groups are phenyl or naphthyl.

The term "heteroaryl or 5 or 6-membered heteroaryl" refers to an aromatic having 5 to 6 ring atoms and containing one or more heteroatoms selected from nitrogen, oxygen or sulphur. Preferred are those heteroaryl groups selected from nitrogen. Examples of such heteroaryl groups include pyridinyl, pyrazinyl, pyrimidinyl or pyridazinyl, and in particular, pyridin-2-yl, pyridin-3-yl, pyridine-4-yl, pyrimidin-5-yl, thiazol-2-yl and thiophen-2-yl as well as those groups which are illustrated with the exemplified compounds of the invention hereinafter.

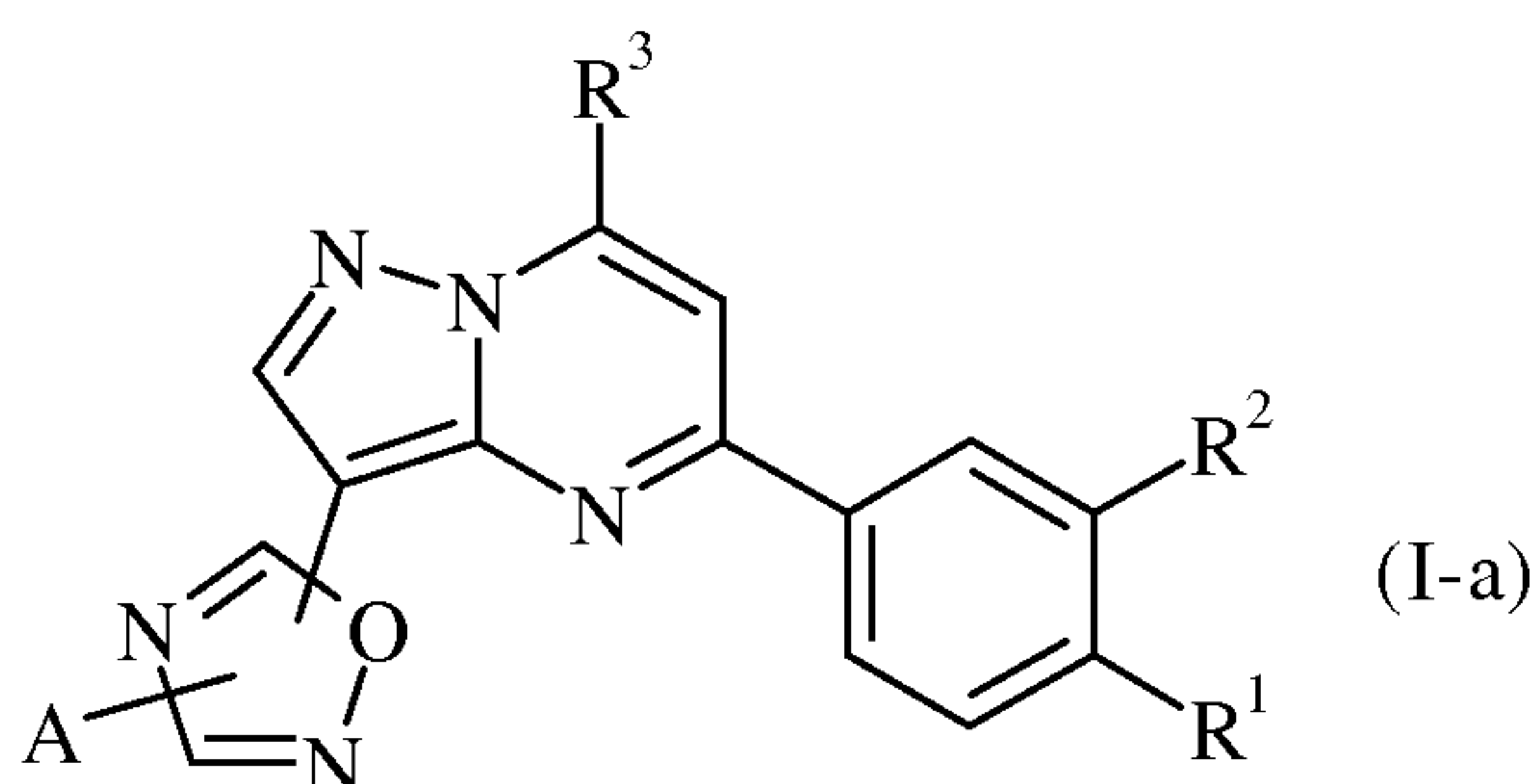
The term "halogen" embraces fluorine (F), chlorine (Cl), bromine (Br) and iodine (I).

The term "cycloalkyl" means a cycloalkyl group containing 3 to 12, preferably 3 to 8 and still more preferably 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. Cycloalkyl containing 3 to 4 carbon atoms are the most preferred.

The term "5 or 6-membered heterocycloalkyl" denotes a heterocyclic ring having 5 or 6 ring members comprising at least two carbon atoms as ring member and 1, 2 or 3 additional heteroatom(s) ring members selected from N, O or S, the remaining ring members being carbon atoms. Examples of 5 or 6 heterocycloalkyl rings include but are not limited to 1*H*-tetrazole; 2*H*-tetrazole; 1,2,3- and 1,2,4-triazole; imidazole; pyrrole; 1,2,3-, 1,3,4- or 1,2,5- thiadiazine; 1,4-oxazine; 1,2- or 1,4-thiazine; 4-morpholinyl; 1-pyrrolidinyl; 1-piperazinyl, preferably 4-morpholinyl; 1-pyrrolidinyl or 1-piperazinyl as well as those groups which are illustrated with the exemplified compounds of the invention hereinafter. Substituents for such 5 or 6 membered heterocyclic ring include but are not limited to halo, amino, nitro, cyano, OH, C₁₋₆-alkyl optionally substituted by OH, C₁₋₆-alkoxy, C₁₋₆-alkenyl, C₃₋₈-cycloalkyl, or CF₃, and preferably C₁₋₆-alkyl or CF₃ as well as those groups which are illustrated with the exemplified compounds of the invention hereinafter.

The term "pharmaceutically acceptable addition salt" refers to any salt derived from an inorganic or organic acid or base.

Also encompassed by the compounds of formula (I) according to the invention are those compounds of formula (I-a):



wherein A and R¹ to R³ are as defined hereinabove in connection with formula (I).

In a certain embodiment the compounds of the invention are those compounds of formula (I-a), wherein:

- R¹ is halo or CF₃;
 - 10 R² is H, halo, C₁₋₆-alkyl or C₁₋₆-alkoxy optionally substituted by one or more F;
 - R³ is H, linear C₁₋₄-alkyl, preferably methyl or C₃₋₄-cycloalkyl, preferably cyclopropyl, which are optionally substituted by 1 to 6 F, preferably by 2 or 3 F;
 - A is selected from the group consisting of aryl, preferably phenyl or 5 or 6-membered heteroaryl, preferably thiophenyl, pyridinyl, pyrimidinyl or pyrazolyl,
 - 15 optionally substituted by one to four R^a;
 - R^a is amino or SO₂-NR^dR^e; with R^d and R^e are H;
- as well as pharmaceutically acceptable salts thereof.

Preferred compounds of formula (I-a) are those compounds of formula (I-a), wherein:

- 20 R¹ is Cl, F or CF₃;
- R² is H, F, Cl, methyl, OEt, CHF₂, CF₃, OCF₃ or OCH₂CF₃;
- R³ is H, methyl or cyclopropyl, which are optionally substituted by 2 or 3 F;
- A is selected from the group consisting of phenyl, thiophenyl, pyridinyl, pyrimidinyl or pyrazolyl, optionally substituted by one R^a;
- 25 R^a is amino or SO₂-NR^dR^e; with R^d and R^e are H;

as well as pharmaceutically acceptable salts thereof, for example the following compounds:

- 4-{5-[7-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 3-{5-[7-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 5 3-(3-Pyridin-3-yl-[1,2,4]oxadiazol-5-yl)-7-trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine;
- 4-{5-[7-Difluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 3-{5-[7-Difluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 10 3-{5-[5-(4-Chloro-phenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 3-{5-[7-Cyclopropyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 15 4-{5-[5-(4-Chloro-phenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 4-{5-[7-Cyclopropyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 3-{5-[5-(4-Chloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 20 4-{5-[5-(4-Chloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 4-{3-[7-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-5-yl}-benzenesulfonamide;
- 25 3-{3-[7-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-5-yl}-benzenesulfonamide;
- 3-(5-{5-[3-(2,2,2-Trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 3-{5-[5-(3-Methyl-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 30 a)pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 4-{5-[5-(3-Methyl-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 3-{5-[5-(4-Chloro-phenyl)-7-difluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;

- 5- {5-[5-(4-Chloro-phenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide;
- 5- {5-[5-(3-Methyl-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-
a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide;
- 5 5-(5-{5-[3-(2,2,2-Trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-7-trifluoromethyl-
pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl)-thiophene-2-sulfonic acid amide;
- 5- {5-[7-Cyclopropyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-
yl]-[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide;
- 4- {5-[7-Trifluoromethyl-5-(3-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-
10 3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 3- {5-[7-Trifluoromethyl-5-(3-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-
3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 5- {5-[7-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-
3-yl]-[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide;
- 15 5- {5-[5-(4-Chloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide;
- 5- {5-[5-(4-Chloro-phenyl)-7-difluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide;
- 5- {5-[7-Methyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-
20 [1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide;
- 5- {5-[7-Difluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-
yl]-[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide;
- 5- {5-[5-(4-Chloro-phenyl)-7-methyl-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide;
- 25 5- {3-[7-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-
3-yl]-[1,2,4]oxadiazol-5-yl}-thiophene-2-sulfonic acid amide;
- 5- {5-[7-Trifluoromethyl-5-(3-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-
3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 5- {5-[7-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-
30 3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 5- {5-[7-Difluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-
yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 5- {5-[5-(3-Methyl-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-
a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;

3-{5-[5-(4-Chloro-phenyl)-7-methyl-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;

5-{5-[7-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-
3-yl]-[1,2,4]oxadiazol-3-yl}-pyrimidin-2-ylamine;

5 3-{5-[5-(4-Chloro-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-
benzenesulfonamide;

5-{5-[5-(4-Trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide;

10 3-{5-[5-(4-Trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;

4-{5-[7-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-
3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;

4-{5-[5-(4-Trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;

15 5-{5-[5-(4-Chloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;

5-{5-[5-(4-Chloro-phenyl)-7-difluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;

20 5-{5-[5-(4-Chloro-3-methyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-
3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;

5-{5-[7-Difluoromethyl-5-(3-methyl-4-trifluoromethyl-phenyl)-pyrazolo[1,5-
a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;

5-{5-[5-(3,4-Dichloro-phenyl)-7-difluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;

25 5-{5-[5-(3,4-Dichloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;

5-{5-[7-Difluoromethyl-5-(3-ethoxy-4-trifluoromethyl-phenyl)-pyrazolo[1,5-
a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;

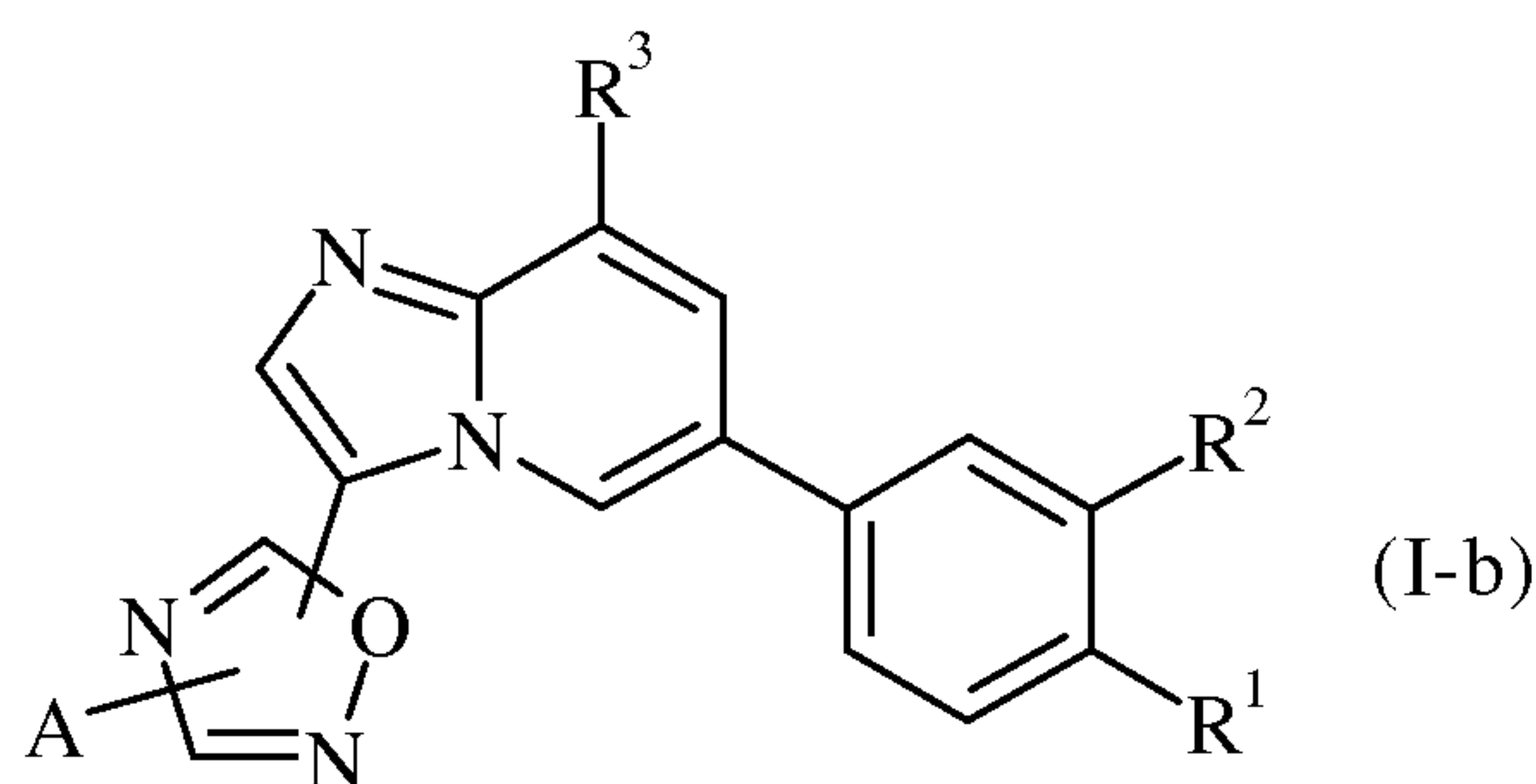
30 a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;

5-(5-{5-[3-(2,2,2-Trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-7-trifluoromethyl-
pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl)-pyridin-2-ylamine;

5-(5-{7-Difluoromethyl-5-[3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-
pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl)-pyridin-2-ylamine;

- 5- {5-[5-(3-Chloro-4-trifluoromethyl-phenyl)-7-difluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 5- {5-[5-(3-Chloro-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 5 5- {5-[7-Difluoromethyl-5-(3-fluoro-4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 5- {5-[5-(3-Fluoro-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 5- {5-[5-(3,4-Difluoro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 10 [1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 5- {5-[5-(4-Chloro-3-methyl-phenyl)-7-difluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 5- {5-[5-(3,4-Difluoro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyrimidin-2-ylamine;
- 15 5- {5-[5-(3-Fluoro-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyrimidin-2-ylamine;
- 5- {5-[5-(3-Chloro-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyrimidin-2-ylamine;
- 5- {5-[5-(3,4-Dichloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyrimidin-2-ylamine;
- 20 [1,2,4]oxadiazol-3-yl}-pyrimidin-2-ylamine;
- 5- {5-[5-(4-Chloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyrimidin-2-ylamine;
- 5- {5-[5-(3-Methyl-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyrimidin-2-ylamine;
- 25 5- {5-[5-(4-Chloro-3-methyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyrimidin-2-ylamine;
- 4- {5-[5-(4-Chloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 4- {5-[5-(3,4-Dichloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine; and
- 30 [1,2,4]oxadiazol-3-yl}-pyridine-2-ylamine.
- 4- {5-[5-(3-Methyl-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridine-2-ylamine.

Also encompassed by the compounds of formula (I) according to the invention are those compounds of formula (I-b):



wherein A and R¹ to R³ are as defined hereinabove in connection with formula (I).

In a certain embodiment the compounds of the invention are those compounds of formula (I-b), wherein:

- 5 R¹ is halo or CF₃;
 R² is H, halo, C₁₋₆-alkyl or C₁₋₆-alkoxy optionally substituted by one or more F;
 R³ is H, linear C₁₋₄-alkyl, preferably methyl or C₃₋₄-cycloalkyl, preferably cyclopropyl, which are optionally substituted by 1 to 6 F, preferably by 2 or 3 F;
 A is selected from the group consisting of aryl, preferably phenyl or 5 or 6-
 10 membered heteroaryl, preferably thiophenyl, pyridinyl, pyrimidinyl or pyrazolyl, optionally substituted by one to four R^a;
 R^a is amino or SO₂-NR^dR^e; with R^d and R^e are H;
 as well as pharmaceutically acceptable salts thereof.

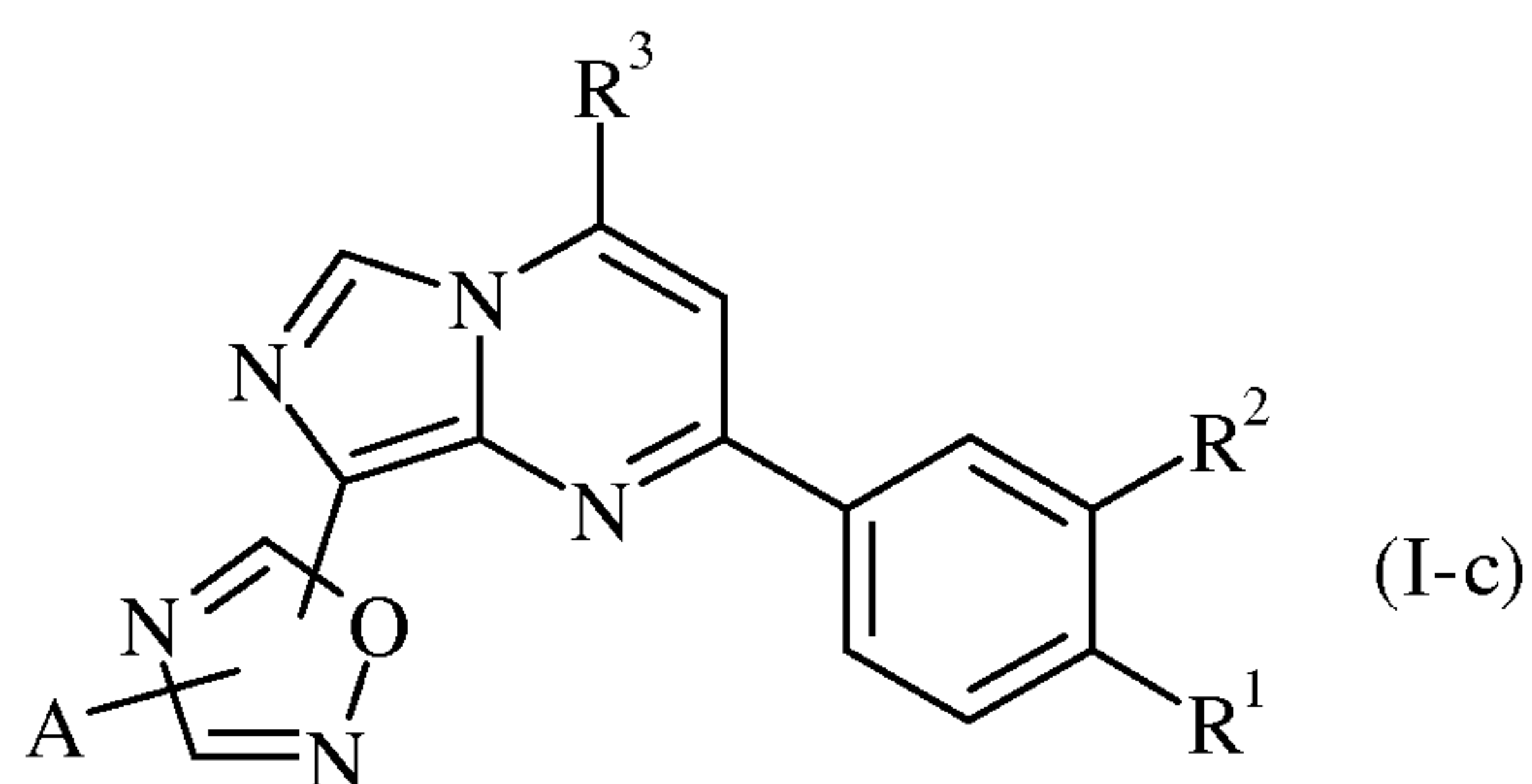
Preferred compounds of formula (I-b) are those compounds of formula (I-b),
 15 wherein:

- R¹ is Cl, F or CF₃;
 R² is H, F, Cl, methyl, OEt, CHF₂, CF₃, OCF₃ or OCH₂CF₃;
 R³ is H, methyl or cyclopropyl, which are optionally substituted by 2 or 3 F;
 A is selected from the group consisting of phenyl, thiophenyl, pyridinyl, pyrimidinyl
 20 or pyrazolyl, optionally substituted by one R^a;
 R^a is amino or SO₂-NR^dR^e; with R^d and R^e are H;
 as well as pharmaceutically acceptable salts thereof, for example the following compounds:

- 3-{5-[8-Trifluoromethyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-
 25 yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
 4-{5-[8-Trifluoromethyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-
 yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;

- 4-{5-[6-(4-Chloro-phenyl)-8-methyl-imidazo[1,2-a]pyridin-3-yl]-
[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 3-{5-[6-(4-Chloro-phenyl)-8-methyl-imidazo[1,2-a]pyridin-3-yl]-
[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 5 5-{5-[6-(4-Chloro-phenyl)-8-methyl-imidazo[1,2-a]pyridin-3-yl]-
[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide;
- 4-{5-[8-Methyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-
[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 3-{5-[8-Methyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-
10 [1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 5-{5-[8-Methyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-
[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide;
- 5-{5-[8-Methyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-
[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 15 5-{5-[8-Methyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-
[1,2,4]oxadiazol-3-yl}-pyrimidin-2-ylamine;
- 4-{5-[6-(4-Trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-[1,2,4]oxadiazol-
3-yl}-benzenesulfonamide;
- 3-{5-[6-(4-Trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-[1,2,4]oxadiazol-
20 3-yl}-benzenesulfonamide;
- 5-{5-[6-(4-Trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-[1,2,4]oxadiazol-
3-yl}-thiophene-2-sulfonic acid amide;
- 5-{5-[6-(4-Chloro-phenyl)-imidazo[1,2-a]pyridin-3-yl]-[1,2,4]oxadiazol-3-yl}-
thiophene-2-sulfonic acid amide;
- 25 5-{5-[6-(4-Trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-[1,2,4]oxadiazol-
3-yl}-pyridin-2-ylamine;
- 5-{5-[6-(4-Chloro-phenyl)-imidazo[1,2-a]pyridin-3-yl]-[1,2,4]oxadiazol-3-yl}-
pyridin-2-ylamine;
- 4-{5-[8-Methyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-
30 [1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine; and
- 4-{5-[6-(4-Trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-[1,2,4]oxadiazol-
3-yl}-pyridin-2-ylamine.

Also encompassed by the compounds of formula (I) according to the invention are those compounds of formula (I-c):



wherein A and R¹ to R³ are as defined hereinabove in connection with formula (I).

In a certain embodiment the compounds of the invention are those compounds of formula (I-c), wherein:

- 5 R¹ is halo or CF₃;
 R² is H, halo, C₁₋₆-alkyl or C₁₋₆-alkoxy optionally substituted by one or more F;
 R³ is H, linear C₁₋₄-alkyl, preferably methyl or C₃₋₄-cycloalkyl, preferably cyclopropyl, which are optionally substituted by 1 to 6 F, preferably by 2 or 3 F;
 A is selected from the group consisting of aryl, preferably phenyl or 5 or 6-
 10 membered heteroaryl, preferably thiophenyl, pyridinyl, pyrimidinyl or pyrazolyl, optionally substituted by one to four R^a;
 R^a is amino or SO₂-NR^dR^e; with R^d and R^e are H;
 as well as pharmaceutically acceptable salts thereof.

Preferred compounds of formula (I-c) are those compounds of formula (I-c),
 15 wherein:

- R¹ is Cl, F or CF₃;
 R² is H, F, Cl, methyl, OEt, CHF₂, CF₃, OCF₃ or OCH₂CF₃;
 R³ is H, methyl or cyclopropyl, which are optionally substituted by 2 or 3 F;
 A is selected from the group consisting of phenyl, thiophenyl, pyridinyl, pyrimidinyl
 20 or pyrazolyl, optionally substituted by one R^a;
 R^a is amino or SO₂-NR^dR^e; with R^d and R^e are H;
 as well as pharmaceutically acceptable salts thereof, for example the following compounds:

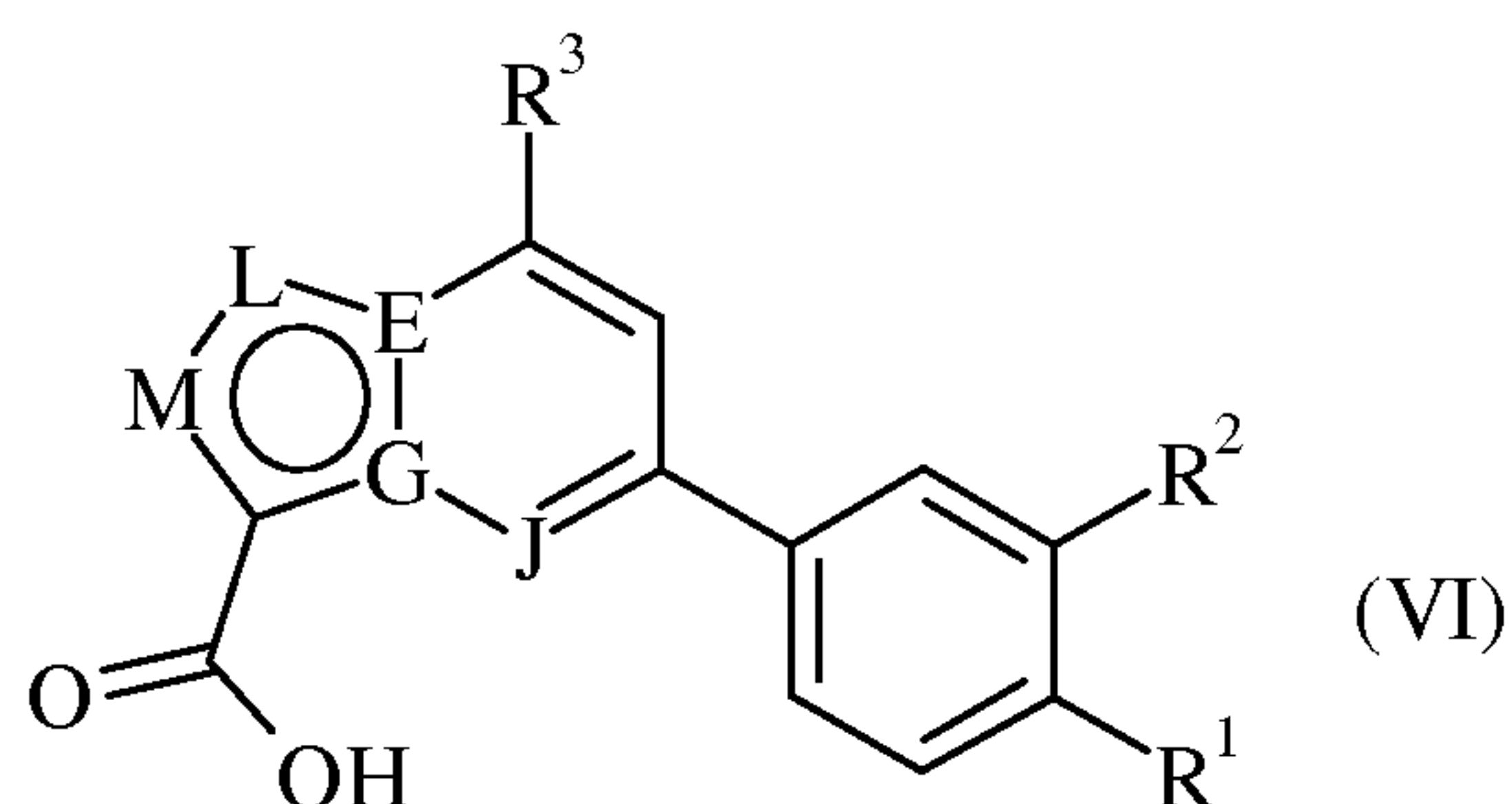
4-{3-[4-Trifluoromethyl-2-(4-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidin-8-
 25 yl]-[1,2,4]oxadiazol-5-yl}-benzenesulfonamide; and

5-{5-[4-Trifluoromethyl-2-(4-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidin-8-
 yl]-[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide.

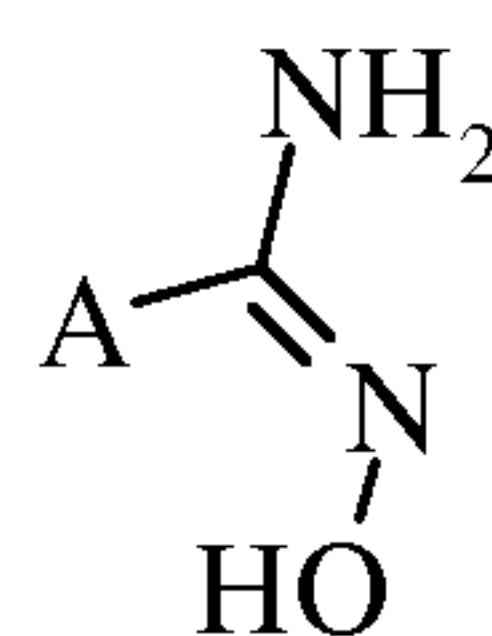
The pharmaceutically acceptable addition salts of the compounds of the invention can be manufactured readily according to methods known per se and taking into consideration the nature of the compound to be converted into a salt. Inorganic or organic acids such as, for example, hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid, phosphoric acid or citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like are suitable for the formation of pharmaceutically acceptable salts of basic compounds of formulae (I), (I-a), (I-b) and (I-c).

The invention also encompasses a process for the preparation of the compounds of formula (I) according to the invention, said process comprising the steps of:

a) either reacting a compound of formula (VI):

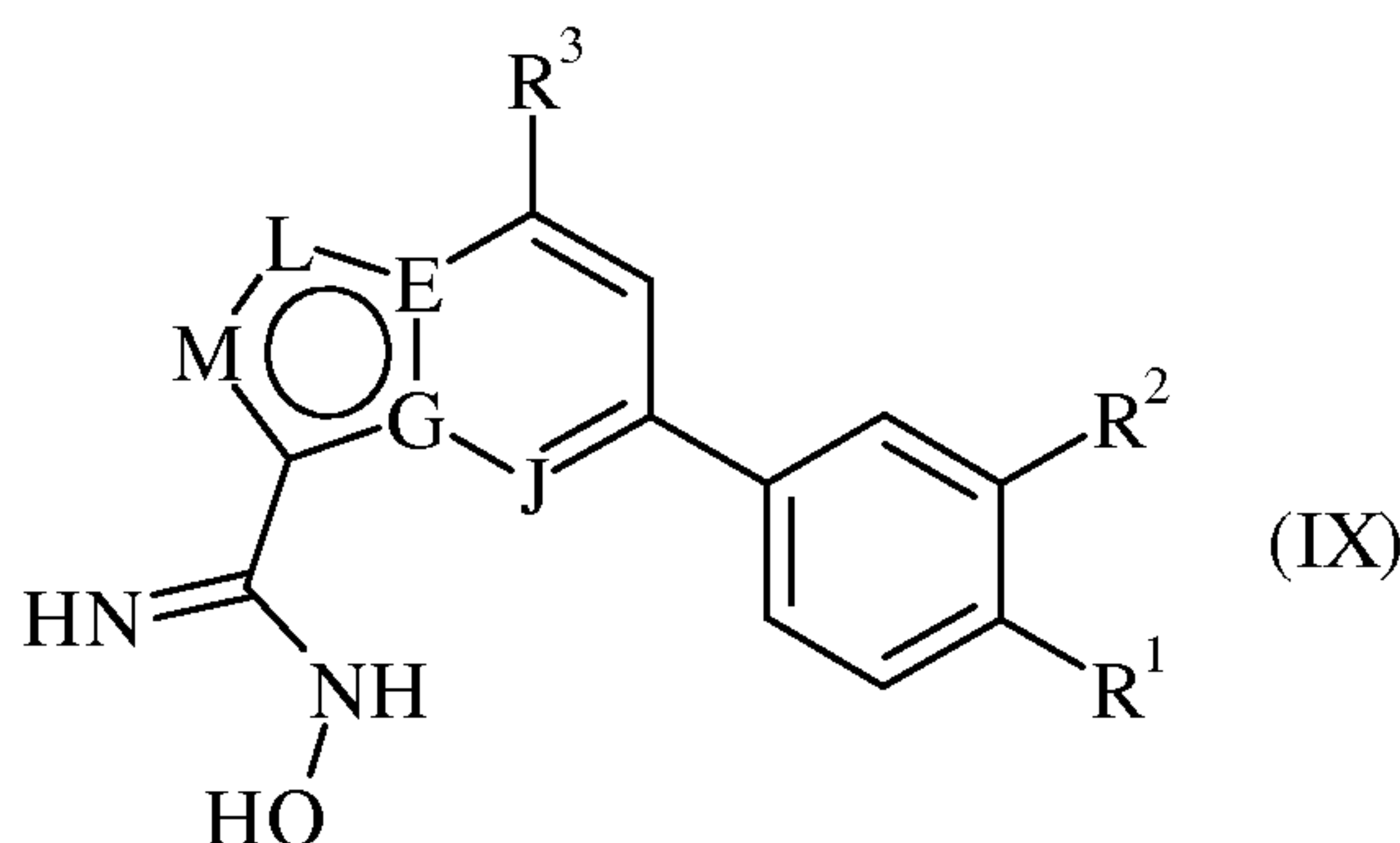


with a compound of formula (VIII):



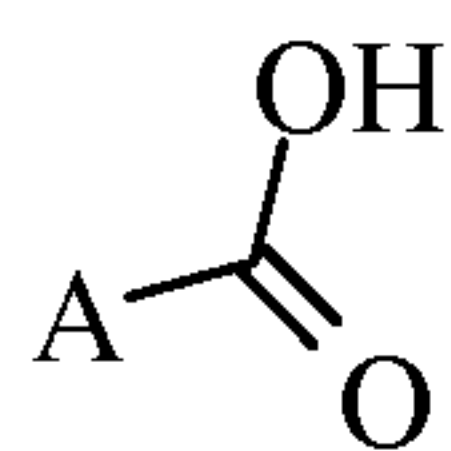
(VIII)

b) or reacting a compound of formula (IX):



with a compound of formulae (X)

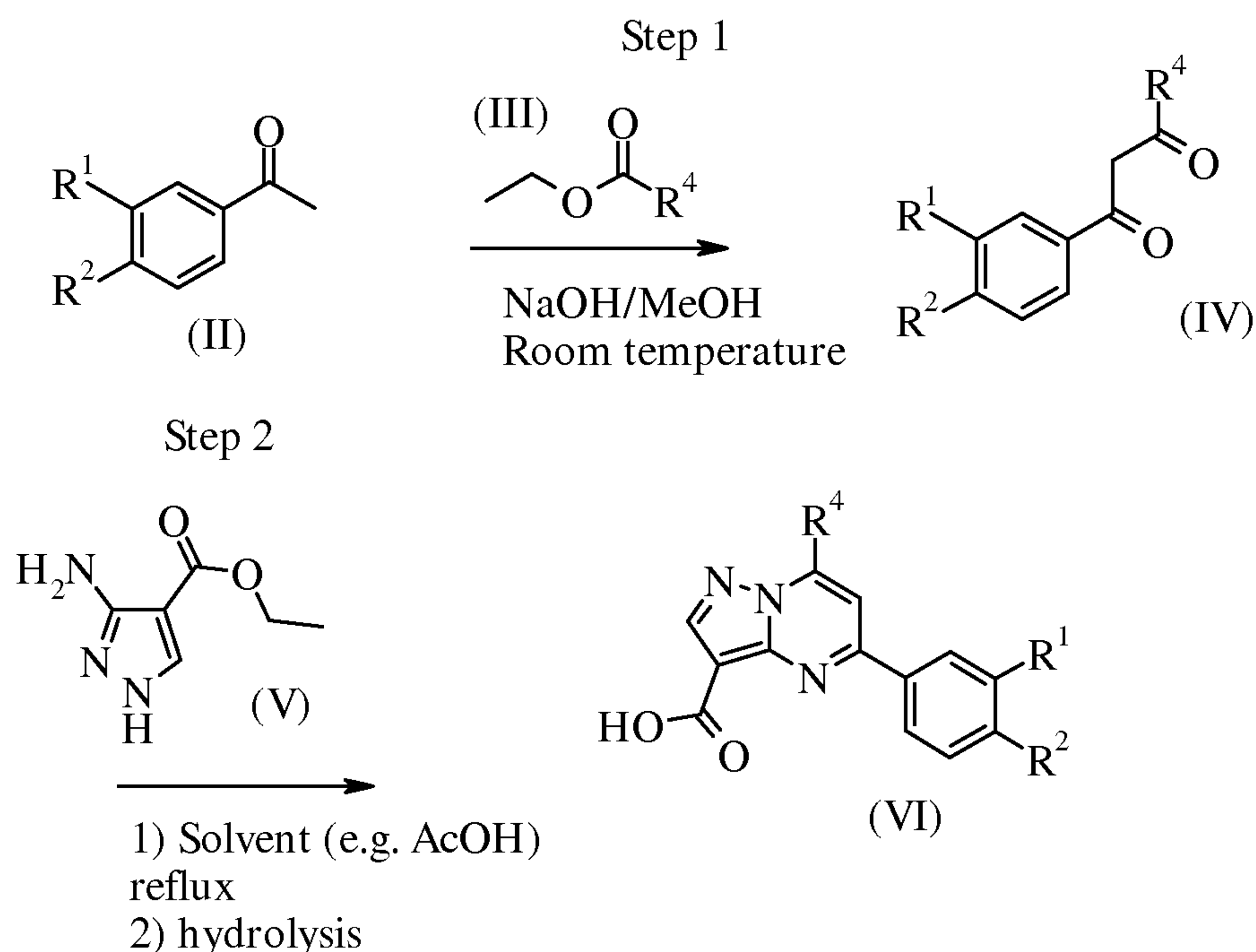
- 14 -



(X)

to obtain a compound of formula (I), wherein R^1 to R^3 and A are as defined hereinabove in connection with formula (I).

The synthesis of the intermediate compounds of formula (VI) above may be carried out in accordance with the following general procedure I, which procedure is outlined below in scheme 1. As for the reaction of the compound of formula (VIII) with the compound of formula (VI), it may be for example carried out in accordance with the following general procedure II which procedure is outlined below in scheme 2. In these schemes, R^1 , R^2 , R^3 , R^4 and p are as defined hereinabove. Procedures I and II are applicable for the preparation of all the compounds according to formula (I). Unless otherwise specified, all the compounds described in general procedures and schemes I and II are commercially available.



General procedure I

15 Step 1:

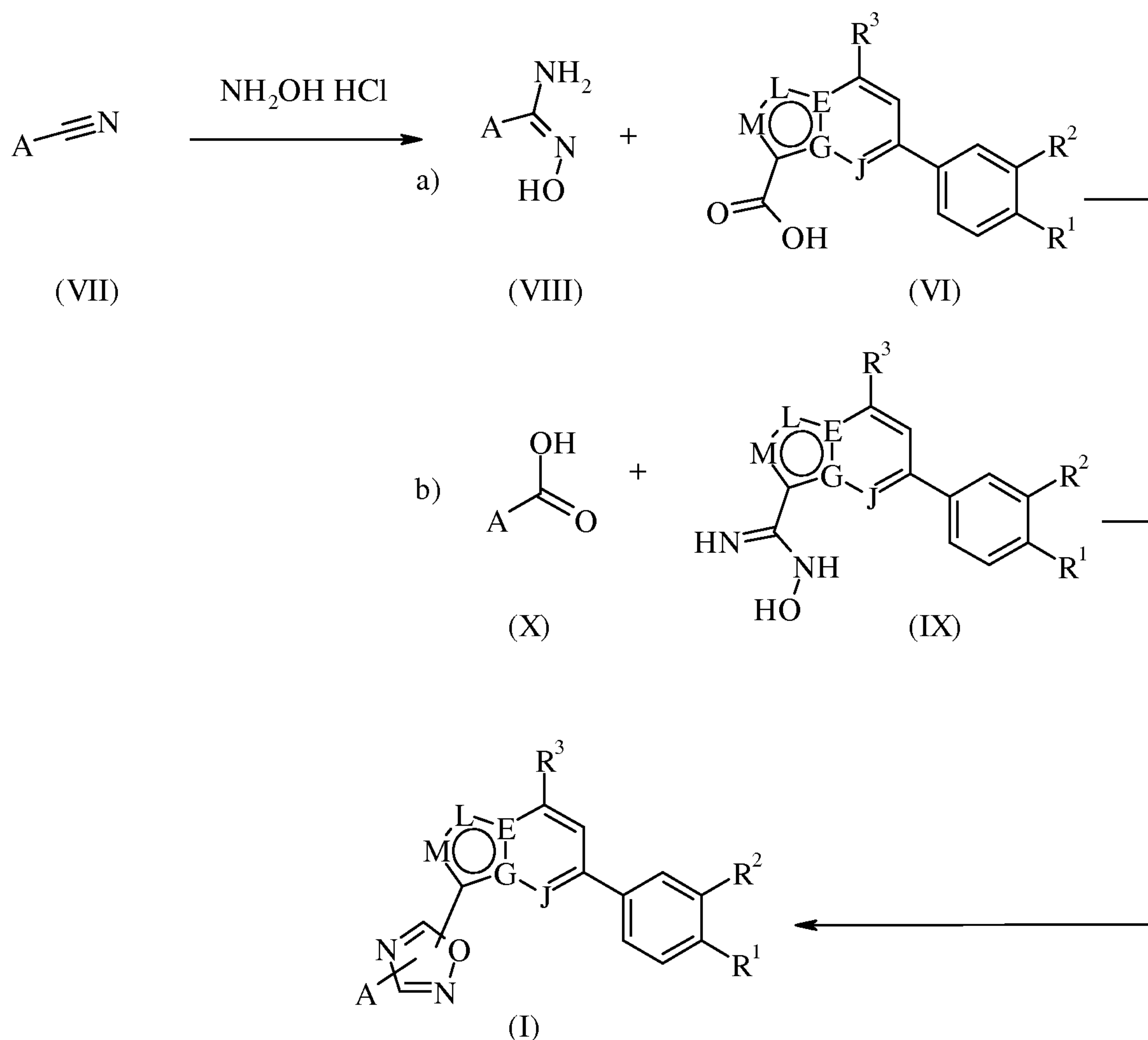
To a stirred solution of commercially available compound of formula (III) in an organic solvent (e.g. tert-butyl-methyl-ether) is added at room temperature a solution of sodium

methanolate in methanol followed by a solution of compound of formula (II) in an organic solvent (e.g. tert-butyl-methyl-ether). The reaction mixture is stirred at room temperature for about 19 h, cooled, acidified and extracted (e.g. with diethyl ether). The combined organic layers are washed and dried (e.g. MgSO_4) and evaporated to give crude
5 the compound of formula (IV) which can be used without further purification.
Compounds of formula (II) are either commercially available or prepared according to examples A.1 to A.6.

Step 2:

A stirred mixture of commercially available compound of formula (V) (e.g. 3-amino-4-ethoxycarbonyl-pyrazole) and compound of formula (IV) in an organic acid (e.g. acetic
10 acid) is heated under reflux conditions for about 1.5 h. The reaction mixture is evaporated and the crude product is dissolved in a mixture of a concentrated base (e.g. KOH in methanol and water). The reaction mixture is stirred at about 60°C for about 1.5 h, cooled, acidified and concentrated. The precipitate is collected by filtration and further
15 purified (e.g. by crystallization from diethylether/methanol) to give the compound of formula (VI).

Scheme 2



General procedure II (oxadiazoles)

The compounds of the invention of formula (I) can be obtained either with route a) or
 5 with route b).

In route a), to a stirred solution of a carboxylic acid (0.5 mmol) in DMF (5 ml) is added at room temperature a compound of formula (VII) (e.g. 1,1'-carbonyl-diimidazol (0.75 mmol)) and the reaction mixture is allowed to stir at room temperature for 2h. The corresponding compound of formula (VIII) (e.g. N-hydroxy-amidine (0.75 mmol)) is
 10 added, the reaction mixture is stirred at 80°C for 15h and evaporated to dryness. Acetic acid (7.5 ml) is added, the stirred reaction mixture heated under reflux conditions for 4h and evaporated. Purification by chromatography on silica gel and crystallization yielded the final product.

In route b) a commercially available carboxylic acid of formula (X) is added a compound of formula (IX). The compounds of formula (IX) are prepared from the corresponding nitriles following the same method as described for the synthesis of compounds of formula (VIII) (see hereinafter: synthesis of intermediates compounds: N-hydroxy-amidines of formulae (VIII) and (IX) and examples B.1 to B.6).

The compounds of formula (I) and their pharmaceutically acceptable salts are metabotropic glutamate receptor antagonists and can be used for the treatment or prevention of acute and/or chronic neurological disorders, such as psychosis, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits. Other treatable indications are restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia. Further treatable indications are acute and chronic pain, Huntington's chorea, ALS, dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficient functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, psychoses, opiate addiction, anxiety, vomiting, dyskinesia, depression, colon cancer, sleep disorders, disorders of circadian rhythms and glioma.

The compounds of formula (I) and pharmaceutically acceptable salts thereof can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. However, the administration can also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula (I) and pharmaceutically acceptable salts thereof can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar, glucose and the like. Adjuvants, such as alcohols, polyols, glycerol, vegetable oils and the like, can be used for aqueous injection solutions of water-soluble salts of compounds of formula (I), but as a

rule are not necessary. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

In addition, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying
5 the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

As mentioned earlier, medicaments containing a compound of formula (I) or a pharmaceutically acceptable salt thereof and a therapeutically inert excipient are also an object of the present invention, as is a process for the production of such medicaments
10 which comprises bringing one or more compounds of formula (I) or pharmaceutically acceptable salts thereof and, if desired, one or more other therapeutically valuable substances into a galenical dosage form together with one or more therapeutically inert carriers.

The dosage can vary within wide limits and will, of course, be fitted to the
15 individual requirements in each particular case. In general, the effective dosage for oral or parenteral administration is between 0.01-20 mg/kg/day, with a dosage of 0.1-10 mg/kg/day being preferred for all of the indications described. The daily dosage for an adult human being weighing 70 kg accordingly lies between 0.7-1400 mg per day, preferably between 7 and 700 mg per day.

20 The present invention relates also to the use of compounds of formula (I) and of pharmaceutically acceptable salts thereof for the production of medicaments, especially for the control or prevention of acute and/or chronic neurological disorders of the aforementioned kind.

The compounds of the present invention are group II mGlu receptor antagonists.
25 The compounds show activities, as measured in the assay described below, of 0.150 μ M or less, typically 0.030 μ M or less, and ideally of 0.010 μ M or less. In the table below are described some specific K_i values of some preferred compounds.

Ex. No.	1	3	11	20	21	34
K_i mGlu2 (μ M)	0.0056	0.0481	0.0088	0.0161	0.0102	0.051
Ex. No.	41	42	46	47	48	77

Ki mGlu2 (μ M)	0.0213	0.0146	0.0145	0.0077	0.0065	0.0255
---------------------	--------	--------	--------	--------	--------	--------

[³H]-LY354740 binding on mGlu2 transfected CHO cell membranes.

Transfection and cell culture

cDNA encoding the rat mGlu2 receptor protein in pBluescript II was subcloned into the
 5 eukaryotic expression vector pcDNA I-amp from Invitrogen Ltd (Paisley, UK). This
 vector construct (pcD1mGR2) was co-transfected with a psvNeo plasmid encoding the
 gene for neomycin resistance, into CHO cells by a modified calcium phosphate method
 described by Chen & Okayama (1988). The cells were maintained in Dulbecco's Modified
 Eagle medium with reduced L-glutamine (2 mM final concentration) and 10 % dialysed
 10 foetal calf serum from Gibco-Invitrogen (Carlsbad, CA, USA). Selection was made in the
 presence of G-418 (1000 ug/ml final) and α -methyl-4-carboxyphenylglycine (MCPG).
 Clones were identified by reverse transcription of 5 μ g total RNA, followed by PCR using
 mGlu2 receptor specific primers 5'-atcactgcttgggtttctggcactg-3' and 5'-
 agcatcactgtgggtggcataggagc-3' in 60 mM Tris HCl (pH 10), 15 mM (NH₄)₂SO₄, 2 mM
 15 MgCl₂, 25 units/ml Taq Polymerase with 30 cycles annealing at 60 °C for 1 min.,
 extension at 72 °C for 30 s, and 1 min. 95 °C denaturation.

Membrane preparation

Cells, cultured as above, were harvested and washed three times with cold PBS and frozen
 at -80 °C. The pellet was resuspended in cold 20 mM HEPES-NaOH buffer containing 10
 20 mM EDTA (pH 7.4), and homogenised with a polytron (Kinematica, AG, Littau,
 Switzerland) for 10 s at 10 000 rpm. After centrifugation for 30 min. at 4 °C, the pellet
 was washed once with the same buffer, and once with cold 20 mM HEPES-NaOH buffer
 containing 0.1 mM EDTA, (pH 7.4). Protein content was measured using the micro BCA
 method from Pierce-Perbio (Rockford, IL, USA) using bovine serum albumin as
 25 standard.

[³H]-LY354740 binding

After thawing, the membranes were resuspended in cold 50mM Tris-HCl buffer
 containing 2 mM MgCl₂ (pH 7) (binding buffer). The final concentration of the
 membranes in the assays was 25 μ g protein/ml. Inhibition experiments were performed
 30 with membranes incubated with 10 nM [³H]-LY354740 at room temperature, for 1 hour,
 in presence of various concentrations of the compound to be tested. Following the
 incubations, membranes were filtered onto Whatmann GF/B glass fiber filters and

washed 5 times with cold binding buffer. Non specific binding was measured in the presence of 10 μ M DCG IV. After transfer of the filters into plastic vials containing 10 ml of Ultima-gold scintillation fluid from Perkin-Elmer(Boston, MA, USA), the radioactivity was measured by liquid scintillation in a Tri-Carb 2500 TR counter (Packard, Zürich, Switzerland).

Data analysis.

The inhibition curves were fitted with a four parameter logistic equation giving IC₅₀ values, and Hill coefficients.

EXAMPLES

Synthesis of starting material

Most of the starting material used in the general procedures I and II is commercially available. However some of said starting material has been prepared according to the procedures as outlined hereafter and unless otherwise specified, the intermediate compounds described therein are novel compounds. The rest of the starting material useful in the general procedures I and II may be prepared taking into account the following examples of preparation and using known methods:

Synthesis of acetophenones derivatives (starting material of formula II)

Example A.1

4-Methyl-3-trifluoromethyl-acetophenone

To a stirred and cooled (0°C) solution of potassium tert.-butanolate (1.39 g, 12 mmol) in DMSO (3 ml) was added diethyl malonate (1.9 ml, 12 mmol) and the reaction mixture was stirred for 20 min at room temperature. To the white suspension was added at room temperature 4-fluoro-3-trifluoromethyl-acetophenone (1 g, 5 mmol) and DMSO (2 ml). The reaction mixture was stirred for 6 h at 60°C and for 16 h at room temperature. The reaction mixture was cooled (0°C), a solution of potassium hydroxide (1.09 g, 19 mmol) in water (2 ml) was added and the mixture was stirred at 100°C for 23 h. The mixture was poured into ice/water (40 ml) and extracted with diethyl ether (2 x 40 ml). The combined organic layers were washed with water (3 x 30 ml), brine (30 ml), dried (MgSO₄) and evaporated. The crude product (0.92 g) was further purified by column chromatography on silica gel (heptane/ethyl acetate 3 : 1) to give the title compound (0.76 g, 77%) as a light yellow liquid. MS (EI) 202.0 [M].

Example A.2

4-Ethoxy-3-trifluoromethyl-acetophenone

To a stirred suspension of potassium ethanolate (2.36 g, 27 mmol) in ethanol (30 ml) was added at room temperature a solution of 4-fluoro-3-trifluoromethyl-acetophenone (2.5 g, 12mmol) in ethanol (10 ml). The reaction mixture was stirred at 60°C for 2 h and evaporated. Ice/2 N HCl (50 ml) was added and the water layer was extracted with diethylether (2x 100 ml). The combined organic layers were washed with ice-water (50 ml), brine (50 ml), dried (MgSO₄) and evaporated to give the title compound (2.9 g, 98%) as a brown solid, which was used without further purification. MS (EI) 232.1 [M].

10

Example A.3

4-(2,2,2-Trifluoro-ethoxy)-3-trifluoromethyl-acetophenone

To a stirred solution of 4-fluoro-3-trifluoromethyl-acetophenone (2.5 g, 12 mmol) in DMSO (15 ml) was added at room temperature 2,2,2-trifluoroethanol (1.7 g, 17 mmol) and potassium hydroxide (1.74 g, 27 mmol). The reaction mixture was stirred for 30 min at 40°C, ice/2N HCl (50 ml) was added and the water layer was extracted with diethylether (2x 100 ml). The combined organic layers were washed with ice-water (50 ml), brine (50 ml), dried (MgSO₄) and evaporated to give the title compound (3.6 g, 98%) as a brown solid, which was used without further purification. MS (EI) 286.1 [M].

Example A.4

3-Methyl-4-trifluoromethyl-acetophenone

The 1-(3-methyl-4-trifluoromethyl-phenyl)-ethanone was prepared by the following sequence:

Step 1: 5-Methyl-2-nitro-4-trifluoromethyl-phenylamine

Under argon atmosphere, a suspension of potassium tert-butanolate (71.6 g, 625 mmol) in DMSO (150 mL) was placed in a 1.5 L flask, fitted with a mechanical stirrer. Then diethyl malonate (97.9 mL, 625 mmol) was added drop wise at 20 - 30 °C under ice bath cooling. To the thick white suspension was the added solid commercially available 5-chloro-2-nitro-4-trifluoromethyl-phenylamine [CAS-No. 35375-74-7] (60.14 g, 250 mmol) in one portion, the mixture was diluted with DMSO (100 mL) and the red solution warmed up to 60 °C and stirred for 20 h at 60 °C. The mixture was cooled to 23 °C and a solution of potassium hydroxide (85%, 65.24 g, 1 mol) in water (100 mL) was

30

added drop wise. The mixture was then heated to 100 °C and stirred for further 4 h. The mixture was cooled to 23 °C, diluted with water (ca. 1000 mL), acidified with 37% HCl 3 to pH 3, and extracted three times with tert-butyl methyl ether (TBME) The organic layers were washed with brine, dried over MgSO₄ and evaporated to give a brown solid, 5 which was triturated with hot heptane, filtered off and washed with heptane to give the title compound as a brown solid (50.0 g, 91%), which was used without further purification. MS (ISN) 218.9 [M-H].

Step 2: 1-Bromo-5-methyl-2-nitro-4-trifluoromethyl-benzene

To a rapidly stirred mixture of tert-butyl nitrite (45.33 mL, 382 mmol) and copper(II) 10 bromide (76.1 g, 341 mmol) in acetonitrile (450 mL) at 65 °C was added cautiously solid 5-methyl-2-nitro-4-trifluoromethyl-phenylamine from step 1 (50.0 g, 227 mmol). After the addition was complete, stirring was continued for further 1 h at 65 °C. The mixture was cooled to 23 °C and poured into 1 N HCl (1000 mL), extracted twice with TBME, the organic layer was washed with brine, dried over MgSO₄. Removal of the solvent in 15 vacuum left a brown oil, which was purified by silica gel column chromatography with heptane/ethyl acetate 9:1 to give the title compound as a yellow liquid (49.8 g, 77%). MS (EI) 283.0 [M] and 285.0 [M⁺2].

Step 3: 5-Methyl-2-nitro-4-trifluoromethyl-benzonitrile

A mixture of 1-bromo-5-methyl-2-nitro-4-trifluoromethyl-benzene from step 2 (49.80 g, 20 175 mmol) and copper(I) cyanide (16.5 g, 184 mmol) in 1-methyl-2-pyrrolidone (NMP) (180 mL) was heated up to 150 °C and stirred for 30 min under nitrogen atmosphere. The mixture was cooled to 23 °C and poured into 1 N HCl, extracted with TBME, washed with brine and dried over Na₂SO₄. Removal of the solvent in vacuum left a brown oil, which was purified by silica gel column chromatography with heptane/ethyl acetate 4:1 - 25 > 2:1 to give the title compound as a light yellow solid (35.48 g, 88%). MS (EI) 230.1 [M].

Step 4: 2-Amino-5-methyl-4-trifluoromethyl-benzonitrile

Iron powder (37.42 g, 670 mmol) was added in small portions to a stirred suspension of finely grinded 5-methyl-2-nitro-4-trifluoromethyl-benzonitrile from step 3 (34.58 g, 150 mmol) in methanol (75 mL) and 37% HCl (93 mL). The internal temperature was kept 30 between 40 and 60 °C by external water bath cooling. The resulting brown solution was stirred for 1 h at 50 °C, giving a green suspension. The mixture was poured into ice cold

water (600 mL), the precipitated solid was filtered off and washed with water to give a green solid, which was dissolved in boiling ethanol (700 mL), activated carbon (ca. 10 g) was added and the mixture was refluxed for 1 h. The hot solution was filtered and the solvent was evaporated in vacuum to leave the title compound as a brown-yellow solid
5 (23.55 g, 78%), which was used without further purification. MS (EI) 200.1 [M].

Step 5: 3-Methyl-4-trifluoromethyl-benzonitrile

To a solution of 2-amino-5-methyl-4-trifluoromethyl-benzonitrile from step 4 (23.34 g, 117 mmol) in dry THF (350 mL) was added isoamyl nitrite (34.3 mL, 257 mmol) and the mixture was refluxed for 20 h. Additional isoamyl nitrite (16.6 mL, 129 mmol) was added
10 and the mixture was refluxed for further 20 h. The mixture was cooled to 23 °C and diluted with TBME, the organic layer was washed with 1 N HCl, sat. NaHCO₃-sol. and brine, dried over Na₂SO₄. Removal of the solvent in vacuum left a brown oil (25.82 g), which was purified by bulb to bulb distillation to give a yellow liquid (20.11 g), which was finally purified by distillation to give the title compound as a yellow liquid (17.10 g, 79%;
15 bp 38-42 °C at 0.8 mbar). MS (EI) 185.1 [M].

Step 6: 3-Methyl-4-trifluoromethyl-benzoic acid

A mixture of 3-methyl-4-trifluoromethyl-benzonitrile from step 5 (16.25 g, 88 mmol) and 3 N NaOH (88 mL, 264 mmol) in dioxane (90 mL) was refluxed for 18 h. The mixture was cooled to 23 °C, diluted with TBME, acidified with 1 N HCl to pH 1 and
20 extracted twice with TBME. The combined organic layers were washed with brine, dried over MgSO₄. Removal of the solvent in vacuum left the title compound as an off white solid (14.46 g, 81%), which was used without further purification. MS (ISN) 203.1 [M-H].

Step 7: N-Methoxy-3,N-dimethyl-4-trifluoromethyl-benzamide

25 To a suspension of 3-methyl-4-trifluoromethyl-benzoic acid from step 6 (14.1 g, 69.1 mmol), N,O-dimethylhydroxylamine hydrochloride (10.78 g, 111 mmol), N-methylmorpholine (12.14 mL, 111 mmol) and 4-DMAP (844 mg, 691 mmol) in DCM (230 mL) at 0 °C were added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (15.98 g, 82.9 mmol) and DMF (85 mL). The mixture was warmed
30 up to 23 °C and was stirred for 18 h under nitrogen atmosphere. The mixture was diluted with TBME, washed with water and twice brine, dried over Na₂SO₄. Removal of the

solvent in vacuum left the title compound as a brown oil (16.92 g, 99%), which was used without further purification. MS (ISP) 248.0 [M⁺H].

Step 8: 1-(3-Methyl-4-trifluoromethyl-phenyl)-ethanone

To a solution of N-methoxy-3,N-dimethyl-4-trifluoromethyl-benzamide from step 7
5 (16.90 g, 68.36 mmol) in THF (280 mL) at -5 °C was added a 3 M methylmagnesium bromide solution in diethyl ether (45.6 mL, 136.7 mmol). The mixture was stirred at 0 °C for 1 h, then was warmed up to 23 °C and stirring was continued at 23 °C for further 1.5 h under nitrogen atmosphere. Then 1 N HCl (100 mL) was added drop wise to the mixture and stirring was continued for 30 min. The mixture was diluted with EtOAc and the
10 aqueous layer was separated, the organic layer was washed with brine and dried over MgSO₄. Removal of the solvent in vacuum left the title compound as a light brown liquid (12.87 g, 93.1%), which was used without further purification. MS (EI) 202.1 [M].

Example A.5

3-Ethoxy-4-trifluoromethyl-acetophenone

15 The 1-(3-ethoxy-4-trifluoromethyl-phenyl)-ethanone was prepared by the following sequence:

Step 1: 5-Ethoxy-2-nitro-4-trifluoromethyl-phenylamine

To EtOH (500 mL) was added potassium metal (ca. 21 g, ca. 537 mmol) and the vigorous reaction had to be cooled with an ice bath. Stirring was continued until all potassium
20 metal was dissolved. Solid commercially available 5-chloro-2-nitro-4-trifluoromethyl-phenylamine [CAS-No. 35375-74-7] (57.74 g, 240 mmol) was added in one portion and the resulting dark red mixture was stirred at 55-60 °C for 4 days. The warm reaction mixture was slowly poured into H₂O (ca. 2000 mL), adjusted pH with conc. HCl to pH 2, the yellow precipitate was filtered off, washed with H₂O and dried in air at 60 °C to give a
25 yellow solid (57.81 g, 96%), which was used without further purification. MS (ISN) 249 [M⁺H].

Step 2: 1-Bromo-5-ethoxy-2-nitro-4-trifluoromethyl-benzene

Solid 5-ethoxy-2-nitro-4-trifluoromethyl-phenylamine from step 1 (57.81 g, 231 mmol) was added slowly over 15 min to a rapidly stirred mixture of tert-butyl nitrite (45.8 mL,
30 347 mmol) and anhydrous copper(II) bromide (77.4 g, 347 mmol) in acetonitrile (462

mL), which was heated to 65 °C in an oil bath. Stirring at 65 °C was continued for 30 min, the reaction mixture was cooled to 23 °C, poured into 1 N HCl, saturated with solid NaCl, extracted with TBME, dried over MgSO₄. Removal of the solvent in vacuum left a dark brown oil (74.5 g). Silica gel column chromatography with heptane/EtOAc 4:1 gave the title compound as a yellow solid (63.03 g, 87%). MS (EI) 313.0 [M] and 315.0 [M⁺2].

Step 3: 5-Ethoxy-2-nitro-4-trifluoromethyl-benzonitrile

A mixture of 1-bromo-5-ethoxy-2-nitro-4-trifluoromethyl-benzene from step 2 (61.81 g, 197 mmol) and CuCN (18.51 g, 207 mmol) in NMP (197 mL) was heated to 150 °C for 30 min. Cooled to 23 °C, poured into 1 N HCl, extracted with TBME, washed with brine, dried over Na₂SO₄. Removal of the solvent in vacuum left a brown oil. Silica gel column chromatography with heptane/EtOAc 4:1 gave the title compound as a yellow solid (46.73 g, 91%). MS (EI) 260.1 [M].

Step 4: 2-Amino-5-ethoxy-4-trifluoromethyl-benzonitrile

Iron powder (40.96 g, 733 mmol) was added in small portions over 5 min to a stirred suspension of finely grinded 5-ethoxy-2-nitro-4-trifluoromethyl-benzonitrile from step 3 (42.79 g, 164.5 mmol) in MeOH (85 mL) and conc. HCl (102 mL) with water bath cooling keeping the internal temperature at 40-50 °C. The resulting mixture was stirred for further 1 h at ca. 50 °C and then poured into ice cold H₂O (700 mL). The precipitate was filtered, washed with water, dried, and dissolved in boiling EtOH (800 mL), activated carbon (ca. 10 g) was added, the mixture was refluxed for 45 min, the hot solution was filtered and evaporated to dryness to leave a yellow solid (31.81 g, 84%), which was used without further purification. MS (EI) 230.1 [M].

Step 5: 3-Ethoxy-4-trifluoromethyl-benzonitrile

To a solution of 2-amino-5-ethoxy-4-trifluoromethyl-benzonitrile from step 4 (31.62 g, 137.4 mmol) in dry THF (410 mL) was added isoamyl nitrite (40.4 mL, 302 mmol) and the mixture was refluxed for 16 h. The solvent was removed in vacuum to give an orange
5 oil, which was dissolved in sat. NaHCO₃-sol., extracted three times with diethyl ether. The combined organic layers were washed with 1 N HCl and brine, dried over Na₂SO₄. Removal of the solvent in vacuum left an orange oil, which was purified by double Kugelrohr distillation (up to 160 °C bath temperature at 1.5 mbar) to give the title compound as a light yellow solid (25.06 g, 85%). MS (EI) 185.1 [M].

10 Step 6: 1-(3-Ethoxy-4-trifluoromethyl-phenyl)-ethanone

To a solution of 3-ethoxy-4-trifluoromethyl-benzonitrile from step 5 (5.00 g, 23.2 mmol), copper(I) bromide (100 mg, 0.7 mmol), tert.-butyldimethylchlorosilane (4.20 g, 27.9 mmol) in dry THF (30 mL) at -70 °C was drop wise added a 3 M methylmagnesium bromide solution in diethyl ether (13.2 mL, 39.6 mmol). The mixture was stirred at -70
15 °C for 10 min, then was warmed up to 0 °C and stirring was continued at 0 °C for further 2 h under nitrogen atmosphere. Poured the reaction mixture onto ice and sat. NH₄Cl-sol., extracted three times with diethyl ether, washed the combined organic layers with brine, dried over MgSO₄. Removal of the solvent in vacuum left a brown oil, which was purified by silica gel column chromatography with heptane/EtOAc 4:1 to give the title
20 compound as a yellow liquid (1.84 g, 34%). MS (EI) 232 [M].

Example A.6

3-(2,2,2-Trifluoro-ethoxy)-4-trifluoromethyl-acetophenone

The 1-[3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-ethanone was prepared by the following sequence:

25 Step 1: 2-Nitro-5-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-phenylamine

Commercially available 5-chloro-2-nitro-4-trifluoromethyl-phenylamine [CAS-No. 35375-74-7] (72.2 g, 300 mmol) was dissolved in DMSO (600 mL) and 2,2,2-trifluoroethanol (270 mL) were added at 23 °C, the slightly exothermic reaction was cooled with a ice bath. KOH (85%, 99.0 g, 1500 mmol) were added slowly and the dark
30 red reaction mixture was stirred at 23 °C for 4 days. Transferred into a 3 L flask and 1500 ml H₂O were added under ice bath cooling, acidified with 3 N HCl and stirred at 23 °C

for 3 h, filtered off the yellow precipitate, washed with H₂O and dried in air at 60 °C to give the title compound as a yellow solid (89.47 g, 98%). MS (ISN) 303.1 [M⁺H].

Step 2: 1-Bromo-2-nitro-5-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-benzene

Solid 2-nitro-5-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-phenylamine from step 1
5 (24.28 g, 80 mmol) was added slowly over 15 min to a rapidly stirred mixture of tert-butyl nitrite (14.23 mL, 120 mmol) and anhydrous copper(II) bromide (26.75 g, 120 mmol) in acetonitrile (160 mL), which was heated to 65 °C in an oil bath. Stirring at 65 °C was continued for 2 h, the reaction mixture was cooled to 23 °C, poured into 1 N HCl, saturated with solid NaCl, extracted with TBME, dried over MgSO₄. Removal of the
10 solvent in vacuum left a dark brown oil (35.57 g). Silica gel column chromatography with heptane/EtOAc 4:1 gave the title compound as an orange solid (30.54 g, 104%), which was used without further purification. MS (EI) 367 [M] and 369 [M⁺2].

Step 3: 2-Nitro-5-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-benzonitrile

A mixture of 1-bromo-2-nitro-5-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-benzene
15 from step 2 (30.54 g, 83.0 mmol) and CuCN (7.80 g, 87.1 mmol) in NMP (83 mL) was heated to 150 °C for 30 min. Cooled to 23 °C, poured into 1 N HCl, extracted with EtOAc, washed with brine, dried over Na₂SO₄. Removal of the solvent in vacuum left a dark brown oil (33.9 g). Silica gel column chromatography with heptane/EtOAc 9:1 -> 4:1 gave the title compound as a yellow solid (22.05 g, 85%). MS (EI) 314 [M].

20 Step 4: 2-Amino-5-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-benzonitrile

Iron powder (15.80 g, 283.0 mmol) was added in small portions over 5 min to a stirred suspension of finely grinded 2-nitro-5-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-benzonitrile from step 3 (19.93 g, 63.4 mmol) in MeOH (32 mL) and conc. HCl (40 mL) with water bath cooling keeping the internal temperature at 25-35 °C. The resulting
25 mixture was stirred for further 1 h at ca. 30 °C and then poured into ice cold H₂O (400 mL). The precipitate was filtered, washed with water, dried, and dissolved in boiling EtOH (400 mL), activated carbon (ca. 10 g) was added, the mixture was refluxed for 45 min, the hot solution was filtered and evaporated to dryness to leave a dark green solid (15.96 g, 84%), which was further purified by silica gel column chromatography with
30 heptane/EtOAc 4:1 to give the title compound as a yellow solid (14.56 g, 81%). MS (ISN) 283 [M-H].

Step 5: 3-(2,2,2-Trifluoro-ethoxy)-4-trifluoromethyl-benzonitrile

To a solution of 2-amino-5-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-benzonitrile from step 4 (14.47 g, 50.9 mmol) in dry THF (153 mL) was added isoamyl nitrite (15.0 mL, 112.0 mmol) and the mixture was refluxed for 20 h. The solvent was removed in vacuum to give an orange oil, which was dissolved in TBME, washed with 1 N HCl, sat. NaHCO₃-sol. and brine, dried over Na₂SO₄. Removal of the solvent in vacuum left a brown solid (15.05 g), which was purified by Kugelrohr distillation (up to 155 °C bath temperature at 1.2 mbar) to give the title compound as a light yellow solid (10.83 g, 79%). MS (EI) 269 [M].

10 Step 6: 3-(2,2,2-Trifluoro-ethoxy)-4-trifluoromethyl-benzoic acid

A mixture of 3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-benzonitrile from step 5 (8.75 g, 33 mmol) and 3 M NaOH (3.9 g, 98 mmol in 33 mL H₂O) in dioxane (33 mL) was refluxed for 7.5 h. Poured onto ice, acidified with conc. HCl to pH 1, saturated with solid NaCl, extracted with TBME, dried over MgSO₄. Removal of the solvent in vacuum left the title compound as an off-white solid (9.22 g, 98%), which was used without further purification. MS (ISN) 286.9 [M-H].

Step 7: N-Methoxy-N-methyl-3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-benzamide

To a mixture of 3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-benzoic acid from step 6 (9.22 g, 32 mmol), N,O-dimethylhydroxylamine hydrochloride (5.00 g, 51 mmol), N-methylmorpholine (5.62 mL, 51 mmol) and 4-DMAP (391 mg, 3.2 mmol) in DCM (100 mL) and DMF (20 mL) at 0 °C was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (7.36 g, 38 mmol) and the mixture was stirred at 23 °C for 18 h. Poured onto ice cold 1 N HCl, extracted with TBME, washed with sat. NaHCO₃-sol. and brine, dried over Na₂SO₄. Removal of the solvent in vacuum left the title compound as a brown oil (10.555 g, 100%), which was used without further purification. MS (EI) 331.0 [M].

Step 8: 1-[3-(2,2,2-Trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-ethanone

To a solution of N-methoxy-N-methyl-3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-benzamide from step 7 (10.467 g, 32 mmol) in THF (100 mL) at -5 °C was added methylmagnesium bromide (3 M in Et₂O, 21.1 mL, 64 mmol). The mixture was stirred at 0 °C for 15 min, then warmed up to 23 °C, stirring was continued for further 1.5 h at 23

°C. Cooled to 0 °C, 1 N HCl (150 mL) was added dropwise, stirring was continued at 23 °C for 15 min, the mixture was diluted with TBME, the phases were separated, the organic layer was washed with water and brine, dried over MgSO₄. Removal of the solvent in vacuum left a yellow solid (9.021 g, 100%), which was used without further purification. MS (EI) 286.1 [M].

Synthesis of intermediates compounds: N-hydroxy-amidines of formulae (VIII) and (IX)

Example B.1

10 N-Hydroxy-7-trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxamidine

A stirred mixture of 7-trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carbonitrile [CAS-No. 851262-50-5] (2.0 g, 5.61 mmol), hydroxylamine hydrochloride (0.78 g, 11.2 mmol) and potassium carbonate (2.33 g, 16.8 mmol) in ethanol (100 ml) was heated under reflux conditions for 3h. After the reaction mixture reached room temperature the precipitate was collected by filtration and washed with ethanol and ethyl acetate. The combined filtrates were evaporated and the crude product purified by flash chromatography on silica gel (ethyl acetate/heptane) to yield the title compound (1.51 g, 69%) as an orange solid. MS (ISP) 389.9 [(M+H)⁺]; mp 252°C.

Example B.2

20 N-Hydroxy-5-sulfamoyl-thiophene-2-carboxamidine

A stirred mixture of 5-sulfamoyl-thiophene-2-carbonitrile [CAS-No. 519055-65-3] (0.31 g, 1.65 mmol), hydroxylamine hydrochloride (0.23 g, 3.31 mmol) and sodium carbonate (0.175 g, 1.65 mmol) in water (4.6 ml) and ethanol (1 ml) was heated under reflux conditions for 1.5h. The reaction mixture was poured into water (50 ml) and extracted with ethyl acetate (3 x 100 ml). The combined organic layers were washed with brine (100 ml), dried (MgSO₄) and evaporated. The crude product was purified by flash chromatography on silica gel (ethyl acetate/heptane) and crystallization (ethyl acetate/MeOH/hexane) to yield the title compound (0.21 g, 58%) as a white solid. MS (ISN) 220.1 [(M-H)⁻]; mp 189°C.

30 Example B.3

N-Hydroxy-4-trifluoromethyl-2-(4-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidine-8-carboxamidine

A stirred mixture of 4-trifluoromethyl-2-(4-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidine-8-carbonitrile [CAS-No. 851263-42-8] 1.16 g, 3.26 mmol), hydroxylamine hydrochloride (0.46 g, 6.62 mmol) and potassium carbonate (1.35 g, 9.77 mmol) in ethanol (50 ml) was heated under reflux conditions for 3h. The precipitate was collected
5 by filtration and washed with ethanol, the combined filtrates were evaporated and the crude product purified by column chromatography on silica gel (ethyl acetate/ethanol 95:5) and crystallization from diethyl ether/hexane to yield the title compound (257 mg, 20%) as a red solid. MS (ISN) 388.2 [(M-H)⁻]; mp 213°C.

Example B.4

10 6-Amino-N-hydroxy-nicotinamide

A stirred mixture of commercially available 2-amino-5-cyano-pyridine [CAS-No. 4214-73-7] (5.0 g, 42 mmol), hydroxylamine hydrochloride (17.5 g, 0.25 mol) and sodium carbonate (31.1 g, 0.29 mol) in water (95 ml) and ethanol (21 ml) was heated under reflux conditions for 6h. The reaction mixture was poured into water (150 ml) and
15 extracted with ethyl acetate (4 x 100 ml). The combined organic layers were washed with brine (150 ml), dried (MgSO₄) and evaporated. The crude product was purified by column chromatography on silica gel (ethyl acetate/MeOH/NH₄OH 4:1:0.5) and crystallization (ethyl acetate/MeOH/hexane) to yield 6-amino-nicotinamide (1.39 g) and the title compound (1.42 g, 22%) as an off-white solid. MS (EI) 152.1 [(M)⁺]; mp 300°C.

20 Example B.5

2-Amino-N-hydroxy-pyrimidine-5-carboxamide

A stirred mixture of commercially available 2-amino-5-cyano-pyrimidine [CAS-No. 1753-48-6] (1.39 g, 11.6 mmol), hydroxylamine hydrochloride (1.61 g, 23.2 mol) and potassium carbonate (4.8 g, 34.7 mol) in ethanol (57 ml) was heated under reflux
25 conditions for 3h. The reaction mixture was evaporated and purified by column chromatography on silica gel (dichloromethane/MeOH 9:1) to yield the title compound (1.28g, 72%) as an off-white solid. MS (EI) 153.1 [(M)⁺]; mp 218°C.

Example B.6

2-Amino-N-hydroxy-pyridine-4-carboxamide

30 A stirred mixture of commercially available 2-amino-4-cyano-pyridine [CAS-No. 42182-27-4] (1.0 g, 8.39 mmol), hydroxylamine hydrochloride (1.17 g, 16.8 mmol) and sodium

carbonate (0.89 g, 8.39 mol) in water (8 ml) and ethanol (16 ml) was heated under reflux conditions for 3h. The reaction mixture was evaporated, water (10 ml) was added and the mixture stirred at room temperature for 1h. The precipitate was collected by filtration to yield the title compound (0.87 g, 68%) as an off-white solid. MS (EI) 152.0 [(M)⁺]; mp

188°C.

Synthesis of intermediates compounds: pyrazolo-pyrimidine carboxylic acids
(intermediates of formula VI) from acetophenones

Some of the intermediates compounds, e.g. the pyrazolo-pyrimidine carboxylic acids derivatives which can be used according to the general procedures I and II are commercially available. However some of said intermediates have been prepared from acetophenones according to the procedures as outlined hereafter and unless otherwise specified, these compounds are novel. The person skilled in the art will be able to prepare other pyrazolo-pyrimidine carboxylic acids derivatives useful in the general procedures I and II taking into account the following examples of preparation:

Example C.1

7-Difluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

a) To a stirred solution of ethyl difluoroacetate (5.0 ml, 21 mmol) in tert-butyl-methyl-ether (30 ml) was added at room temperature a 5.4M solution of sodium methanolate in methanol (4.65 ml, 25 mmol) followed by a solution of commercially available 4-trifluoromethyl-acetophenone (4.0 g, 21 mmol) in tert-butyl-methyl-ether (10 ml). The reaction mixture was stirred at room temperature for 19 h, poured into ice/water (50 ml), acidified with 2N HCl (40 ml) and extracted with diethyl ether (2 x 100 ml). The combined organic layers were washed with brine (2 x 50 ml), dried (MgSO₄) and evaporated to give crude 4,4-difluoro-1-(4-trifluoromethyl-phenyl)-butane-1,3-dione (5.87 g) as a yellow liquid, which was used without further purification.

b) A stirred mixture of commercially available 3-amino-4-ethoxycarbonyl-pyrazole (3.38 g, 22 mmol) and 4,4-difluoro-1-(4-trifluoromethyl-phenyl)-butane-1,3-dione (5.8 g, 22 mmol) in acetic acid (45 ml) was heated under reflux conditions for 1.5 h. The reaction mixture was evaporated and the crude product (yellow solid, 8.5 g, 22 mmol) was dissolved in a mixture of 2M KOH in methanol (176.5 ml, 0.35 mol) and water (85 ml). The reaction mixture was stirred at 60°C for 1.5 h, poured into ice/water (200 ml), acidified with 3N sulfuric acid (pH = 4) and stirred at room temperature for 30 min. The

precipitate was collected by filtration and further purified by crystallization from diethylether/methanol to give the title compound (4.51 g, 57%) as an off-white solid. MS (ISP) 356.1 [(M-H)⁻]; m.p. 261°C.

Example C.2

5 7-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

The title compound was prepared from commercially available ethyl trifluoroacetate, commercially available 4-trifluoromethyl-acetophenone and commercially available 3-amino-4-ethoxycarbonyl-pyrazole according to the general procedure I.

10 Light yellow solid. MS (EI) 374.9 [M]; mp 248°C.

Example C.3

5-(4-Chloro-phenyl)-7-difluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

The title compound was prepared from commercially available ethyl difluoroacetate, commercially available 4-chloro-acetophenone and commercially available 3-amino-4-ethoxycarbonyl-pyrazole according to the general procedure I. Off-white solid. MS (ISP) 322.2 [(M-H)⁻]; mp 232°C.

Example C.4

5-(4-Chloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

The title compound was prepared from commercially available ethyl trifluoroacetate, commercially available 4-chloro-acetophenone and commercially available 3-amino-4-ethoxycarbonyl-pyrazole according to the general procedure I. Off-white solid. MS (ISP) 340.0 [(M-H)⁻]; mp 238°C.

Example C.5

25 7-Difluoromethyl-5-(3-methyl-4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

The title compound was prepared from commercially available ethyl difluoroacetate, 3-methyl-4-trifluoro-acetophenone (example A.4) and commercially available 3-amino-4-ethoxycarbonyl-pyrazole according to the general procedure I. Off-white solid. MS (ISP) 370.1 [(M-H)⁻]; mp 217°C.

- 33 -

Example C.6

5-(4-Chloro-3-methyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

The title compound was prepared from commercially available ethyl trifluoroacetate,
5 commercially available 4-chloro-3-methyl-acetophenone and commercially available 3-amino-4-ethoxycarbonyl-pyrazole according to the general procedure I. Off-white solid. MS (ISP) 354.0 [(M-H)⁻]; mp 243°C.

Example C.7

5-(3,4-Dichloro-phenyl)-7-difluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

10 The title compound was prepared from commercially available ethyl difluoroacetate, commercially available 3,4-dichloro-acetophenone and commercially available 3-amino-4-ethoxycarbonyl-pyrazole according to the general procedure I. Off-white solid. MS (ISP) 356.0 [(M-H)⁻]; mp 263°C.

Example C.8

15 5-(3-Methyl-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

The title compound was prepared from commercially available ethyl trifluoroacetate, 3-methyl-4-trifluoro-acetophenone (example A.4) and commercially available 3-amino-4-ethoxycarbonyl-pyrazole according to the general procedure I. Off-white solid. MS (ISP)
20 388.1 [(M-H)⁻]; mp 250°C.

Example C.9

5-(3,4-Dichloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

The title compound was prepared from commercially available ethyl trifluoroacetate, commercially available 3,4-dichloro-acetophenone and commercially available 3-amino-
25 4-ethoxycarbonyl-pyrazole according to the general procedure I. Light yellow solid. MS (ISP) 374.1 [(M-H)⁻]; mp 264°C.

- 34 -

Example C.10

5-[3-(2,2,2-Trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

The title compound was prepared from commercially available ethyl trifluoroacetate, 3-
5 (2,2,2-trifluoroethoxy-4-trifluoro-acetophenone (Example A.6) and commercially available 3-amino-4-ethoxycarbonyl-pyrazole according to the general procedure I. Off-white solid. MS (ISP) 471.9 [(M-H)⁻]; mp 264°C.

Example C.11

5-(3-Ethoxy-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-
10 carboxylic acid

The title compound was prepared from commercially available ethyl trifluoroacetate, 3-ethoxy-4-trifluoro-acetophenone (Example A.5) and commercially available 3-amino-4-ethoxycarbonyl-pyrazole according to the general procedure I. Off-white solid. MS (ISP) 418.0 [(M-H)⁻]; mp 264°C.

15 Example C.12

7-Difluoromethyl-5-(3-ethoxy-4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

The title compound was prepared from commercially available ethyl difluoroacetate, 3-ethoxy-4-trifluoro-acetophenone (Example A.5) and commercially available 3-amino-4-
20 ethoxycarbonyl-pyrazole according to the general procedure I. Yellow solid. MS (ISP) 400.2 [(M-H)⁻]; mp 247°C.

Example C.13

5-(4-Chloro-3-methyl-phenyl)-7-difluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

25 The title compound was prepared from commercially available ethyl difluoroacetate, commercially available 4-chloro-3-methyl-acetophenone and commercially available 3-amino-4-ethoxycarbonyl-pyrazole according to the general procedure I. Light yellow solid. MS (ISP) 336.0 [(M-H)⁻]; mp 238°C.

- 35 -

Example C.14

7-Difluoromethyl-5-[3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-
pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

The title compound was prepared from commercially available ethyl difluoroacetate, 3-
5 (2,2,2-trifluoroethoxy-4-trifluoro-acetophenone (Example A.6) and commercially
available 3-amino-4-ethoxycarbonyl-pyrazole according to the general procedure I. Off-
white solid. MS (ISP) 454.2 [(M-H)⁻]; mp 261°C.

Example C.15

5-(3-Chloro-4-trifluoromethyl-phenyl)-7-difluoromethyl-pyrazolo[1,5-a]pyrimidine-3-
10 carboxylic acid

The title compound was prepared from commercially available ethyl difluoroacetate, 3-
chloro-4-trifluoromethyl-acetophenone [CAS-No. 129322-80-1] and commercially
available 3-amino-4-ethoxycarbonyl-pyrazole according to the general procedure I.
Light red solid. MS (ISP) 390.2 [(M-H)⁻]; mp 216°C.

15 Example C.16

7-Difluoromethyl-5-(3-fluoro-4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-
carboxylic acid

The title compound was prepared from commercially available ethyl difluoroacetate,
commercially available 3-fluoro-4-trifluoromethyl-acetophenone and commercially
20 available 3-amino-4-ethoxycarbonyl-pyrazole according to the general procedure I.
Light brown solid. MS (ISP) 374.1 [(M-H)⁻]; mp 233°C.

Example C.17

5-(3-Chloro-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-
carboxylic acid

25 The title compound was prepared from commercially available ethyl trifluoroacetate, 3-
chloro-4-trifluoromethyl-acetophenone [CAS-No. 129322-80-1] and commercially
available 3-amino-4-ethoxycarbonyl-pyrazole according to the general procedure I.
Light yellow solid. MS (ISP) 408.0 [(M-H)⁻]; mp 244°C.

Example C.18

- 36 -

5-(3-Fluoro-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

The title compound was prepared from commercially available ethyl trifluoroacetate, commercially available 3-fluoro-4-trifluoromethyl-acetophenone and commercially available 3-amino-4-ethoxycarbonyl-pyrazole according to the general procedure I.
Light yellow solid. MS (ISP) 392.0 [(M-H)⁻]; mp 212°C.

Example C.19

5-(4-Trifluoromethoxy-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

The title compound was prepared from commercially available ethyl trifluoroacetate, commercially available 4-trifluoromethoxy-acetophenone and commercially available 3-amino-4-ethoxycarbonyl-pyrazole according to the general procedure I.
White solid. MS (ISP) 390.0 [(M-H)⁻]; mp 225°C.

Example C.20

7-Difluoromethyl-5-(4-trifluoromethoxy-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

The title compound was prepared from commercially available ethyl difluoroacetate, commercially available 4-trifluoromethoxy-acetophenone and commercially available 3-amino-4-ethoxycarbonyl-pyrazole according to the general procedure I.
Off-white solid. MS (ISP) 372.1 [(M-H)⁻]; mp 231°C.

Example C.21

5-(3,4-Difluoro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

The title compound was prepared from commercially available ethyl trifluoroacetate, commercially available 3,4-difluoro-acetophenone and commercially available 3-amino-4-ethoxycarbonyl-pyrazole according to the general procedure I.
Light yellow solid. MS (ISP) 342.0 [(M-H)⁻]; mp 274°C.

Example C.22

5-(4-Chloro-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

a. A mixture of ethyl 3-(4-chloro-phenyl)-3-oxo-propionate (18.1 g, 0.080 mol) and ethyl 5-amino-1H-pyrazole-4-carboxylate (13.7 g, 0.088 mol) was stirred at for 3

- h 160 °C. Ethyl acetate (40 mL) and hexane (40 mL) were successively added to the cooled mixture and stirring was continued at 0 °C for 0.5 h. The crystals were isolated by filtration and triturated for 1.2 h with 0.2 N HCl (80 mL). The solid was filtered off, washed with water and dried to give ethyl 5-(4-chloro-phenyl)-7-hydroxy-pyrazolo[1,5-a]pyrimidine-3-carboxylate (13.3 g, 52%). White solid. MS (ISN) 316.3 [(M-H)⁻]; mp 190-192 °C.
- 5 b. A mixture of 5-(4-chloro-phenyl)-7-hydroxy-pyrazolo[1,5-a]pyrimidine-3-carboxylate (9.53 g, 0.03 mol), phosphorous oxychloride (11.0 mL, 0.12 mol), and N,N-dimethylaniline (1.3 mL, 0.01 mol) was stirred for 2 h at 100 °C. The mixture was evaporated in vacuo and the residue was partitioned between water and dichloromethane. The organic phase was washed with water, dried (Na₂SO₄) and evaporated in vacuo. The remaining solid was crystallized from ethyl acetate/hexane to give 7-chloro-5-(4-chloro-phenyl)-pyrazolo[1,5-a]pyrimidine (6.80 g, 67%). Pale-yellow solid, MS (ISP) 336.0 [(M+H)⁺]; mp 133-135 °C.
- 10 c. A mixture of 7-chloro-5-(4-chloro-phenyl)-pyrazolo[1,5-a]pyrimidine (0.34g, 1.0 mmol), triethylamine (0.28 mL, 2.0 mmol), and 5% palladium-charcoal (0.03 g) in ethanol (60 mL) was stirred in an atmosphere of hydrogen for 12 min at 20 °C. The catalyst was removed by filtration and the solution was evaporated. The residue was partitioned between ethyl acetate and water and the organic layer was dried (Na₂SO₄) and evaporated in vacuo. The residue was crystallized from ethyl acetate/cyclohexane to give ethyl 5-(4-chloro-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylate (0.18 g, 59%). Off-white solid; MS (ISP) 301.9 [(M+H)⁺].
- 15 d. A mixture of ethyl 5-(4-chloro-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylate (0.12 g, 0.4 mmol) and 0.5 N sodium hydroxide solution (4 mL) in methanol (4 mL) was heated to 70 °C for 2 h. The mixture was cooled, diluted with water (8 mL) and concentrated in vacuo. The aqueous solution was acidified to pH 2 by the addition of 3N HCl. The precipitate was isolated by filtration, washed with water, and dried to give 5-(4-chloro-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (0.11 g, 100%). Off-white solid. MS (ISN) 272.3 [(M-H)⁻]; mp 309-311 °C
- 20
25
30

Example C.23

5-(4-Trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

By subjecting ethyl 3-(4-trifluoro-phenyl)-3-oxo-propionate in analogous manner to the procedures described in example C.22, steps a-d, the title compound was obtained. White

solid. NMR (DMSO-d₆): d 7.97/8.52 (2 d, 2 x 2H), 7.98/9.41 (2 d, 2 x 1 H), 8.63 (s, 1H), 12.46 (s, 1H) ppm.

Example C.24

5-(4-Chloro-phenyl)-7-methyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

5 To a solution of 7-chloro-5-(4-chloro-phenyl)-pyrazolo[1,5-a]pyrimidine (0.34 g, 1.0 mmol) and tetrakis(triphenylphosphin)palladium (0.35 g, 0.3 mmol) in THF (15 mL) was added at 20°C 2 M dimethylzinc/toluene solution (1.3 mL, 3.6 mmol) and the mixture was refluxed in an atmosphere of argon for 2 h. After the slow addition at 0°C of sat. aqueous ammonium chloride solution (10 mL), the mixture was partitioned between
10 ethyl acetate and water. The organic layer was evaporated in vacuo and the residue chromatographed on silica gel using ethyl acetate/hexane (1:2 v/v) as eluent to give ethyl 5-(4-chloro-phenyl)-7-methyl-pyrazolo[1,5-a]pyrimidine-3-carboxylate (0.15 g) as a white solid. This material was saponified using in an analogous manner the procedure described in example C.22, step d), to give the title compound. White solid; MS (ISN)
15 286.0 [(M-H)⁻]; mp 233-235 °C.

Example C.25

7-Methyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

Subjecting ethyl 3-(4-trifluoro-phenyl)-3-oxo-propionate in analogous manner to the procedures described in Example C.22, steps a-b, and applying to the resulting product
20 the procedure described in example C.24, afforded the title compound. White solid. MS (ISP) 320.3 [(M-H)⁻]; mp 244-245 °C.

Example C.26

5-(4-Chloro-phenyl)-7-ethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

To a solution of 7-chloro-5-(4-chloro-phenyl)-pyrazolo[1,5-a]pyrimidine (1.0 g, 3.0
25 mmol), tetrakis(triphenylphosphin)palladium (0.35 g, 0.3 mmol) in THF (5 mL) was added at 20°C 0.4 M ethylzinc chloride/THF solution (30 mL, 12 mmol; freshly prepared by stirring a mixture of 6 mL of 2 M ethylmagnesium chloride/THF and 24 mL of 0.5 M zinc chloride/THF for 1 h at 0°C followed by 1 h at 20°C) and the mixture was refluxed in an atmosphere of argon for 2 h. After the slow addition at 0 °C of sat. aqueous
30 ammonium chloride solution (8 mL), the mixture was partitioned between ethyl acetate and 10% sodium chloride solution. The organic layer was evaporated in vacuo and the

residue chromatographed on silica gel using ethyl acetate/ cyclo-hexane (1:4 v/v) as eluent to give ethyl 5-(4-chloro-phenyl)-7-ethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (0.53 g, 54%). This material was saponified using in an analogous manner the procedure described in example C.22, step d), to give the title compound. White solid; MS (ISN)

5 330.1 [(M-H)⁻]; mp 227 °C.

Example C.27

5-(4-Chloro-phenyl)-7-propyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

Subjecting ethyl 7-chloro-5-(4-chloro-phenyl)-pyrazolo[1,5-a]pyrimidine in analogous manner to the procedure described in Example C.26, but replacing the ethylzinc chloride/THF solution by a 0.4 M propylzinc chloride/THF solution (freshly prepared from ethylmagnesium chloride and zinc chloride), the title compound was obtained. White solid. MS (ISN) 314.1 [(M-H)⁻]; mp 208 °C.

Example C.28

5-(4-Chloro-phenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

15 To a solution of 7-chloro-5-(4-chloro-phenyl)-pyrazolo[1,5-a]pyrimidine (4.0 g, 12.0 mmol), tetrakis(triphenylphosphin)palladium (1.15 g, 1.0 mmol) in THF (20 mL) was added at 20°C 0.25 M cyclopropylzinc chloride/THF suspension (ca.192 mL, 48 mol; freshly prepared by stirring a mixture of 96 mL of 0.5 M cyclopropylmagnesium bromide/THF and 96 mL of 0.5 M zinc chloride/THF (96 mL) for 1 h at 0°C followed by 20 1 h at 20°C) and the mixture was refluxed in an atmosphere of argon for 2.5 h. After the slow addition at 0°C of sat. aqueous ammonium chloride solution (30 mL), the mixture was partitioned between ethyl acetate and 10% sodium chloride solution. The organic layer was evaporated in vacuo and the residue chromatographed on silica gel using ethyl acetate/cyclohexane (1:4 v/v) as eluent to give after crystallization from ethyl acetate ethyl 25 5-(4-chloro-phenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (2.54 g, 62%) as an off-white solid, mp 141-143°C. This material was saponified using in an analogous manner the procedure described in example C.22, step d), to give the title compound. Off-white solid, MS (ISN) 312.3 [(M-H)⁻]; mp 242-243 °C.

Example C.29

30 7-Cyclopropyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

By subjecting ethyl 3-(4-trifluoro-phenyl)-3-oxo-propionate in analogous manner to the procedures described in example C.22, steps a-b, and applying to the resulting product the procedure described in example C.28, the title compound was obtained. Off-white solid. MS (ISP) 346.3 [(M-H)⁻]; mp 233-235°C.

5

Example C.30

4-Trifluoromethyl-2-(4-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidine-8-carboxylic acid

1) A stirred solution of commercially available 5-amino-1H-imidazole-4-carboxamide (25 g, 198 mmol) in methanesulfonic acid (107 ml) and ethanol (400 ml) was stirred at
10 reflux conditions for 12d, evaporated and water (300 ml) was added. While stirring and cooling (ice/water) sodium hydroxide solution (32%) was added until pH = 6 was reached. The water layer was saturated with sodium chloride and extracted with ethyl acetate (3 x 200 ml). The combined organic layers were dried (MgSO₄), evaporated and the crude product purified crystallization (ethyl acetate/ethanol) to yield 5-amino-1H-
15 imidazole-4-carboxylic acid ethyl ester (13.7 g, 45%) as a light brown solid. MS (EI) 155.1 [(M)⁺]; mp 178°C.

2) A mixture of 4,4,4-trifluoro-1-(4-trifluoromethyl-phenyl)-butane-1,3-dione (10.0 g, 35.2 mmol) and 5-amino-1H-imidazole-4-carboxylic acid ethyl ester (5.0 g, 32.2 mmol)
20 in acetic acid (120 ml) was refluxed for 24 h and evaporated. The crude product was further purified by column chromatography on silica gel (ethyl acetate/heptane) and crystallization (diethyl acetate/hexane) to yield 4-trifluoromethyl-2-(4-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidine-8-carboxylic acid ethyl ester (5.65 g, 43%) as a yellow solid. MS (EI) 403.1 [(M)⁺]; mp 243°C.

25

3) A mixture of 4-trifluoromethyl-2-(4-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidine-8-carboxylic acid ethyl ester (5.6 g, 13.9 mmol), 2M potassium hydroxide solution (111 ml) and water (55 ml) was stirred at room temperature for 5h, cooled (ice-water), and acetic acid (30 ml) was added. The mixture was evaporated, acetic acid (150
30 ml) was added and the stirred solution was heated under reflux conditions for 20 min. The reaction mixture was evaporated, water (150 ml) was added followed by extraction with ethyl acetate (2 x 300 ml). The combined organic layers were washed with brine (2 x 150 ml), dried (MgSO₄) and evaporated. The crude product was further purified by column chromatography on silica gel (ethyl acetate/heptane 1:1) to yield 4-

trifluoromethyl-2-(4-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidine-8-carboxylic acid (1.93 g, 37%) as a yellow solid. MS (ISN) 374.3 [(M-H)⁻]; mp 231°C.

Example C.31

5 7-Trifluoromethyl-5-(3-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

The title compound was prepared from commercially available ethyl trifluoroacetate, commercially available 3-trifluoromethyl-acetophenone and commercially available 3-amino-4-ethoxycarbonyl-pyrazole according to the general procedure I.

Light yellow solid. MS (EI) 375.0 [(M)⁺]; mp 212°C.

10 Example C.32

8-Trifluoromethyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid

Step 1) (4-Methoxy-benzyl)-(3-trifluoromethyl-pyridin-2-yl)-amine

A mixture of 2-chloro-3-trifluoromethylpyridine (64.83 g, 357 mmol), 4-methoxybenzylamine (56 mL, 429 mmol) and DIPEA (73.4 mL, 429 mmol) in n-butanol (100 mL) was refluxed (oil bath temp. 140 °C) for 3.5 days. Concentrated in vacuum, partitioned between 25% HCl and TBME, reextracted the organic layer twice with 25% HCl, the aqueous layer was made alkaline with 32% NaOH, extracted with TBME, washed with brine and dried over Na₂SO₄. Removal of the solvent in vacuum left a brown oil (105.21 g, 104%). Vacuum distillation gave the title compound as a colorless liquid (83.766 g, 83%, 4877-2/2; bp 139-141 °C at 1.4 mbar). MS (ISP) 283.3 [(M+H)⁺].

Step 2) 3-Trifluoromethyl-pyridin-2-ylamine CAS-No. [183610-70-0]

To conc. sulfuric acid (230 mL) at 5 °C was dropwise added above (4-methoxy-benzyl)-(3-trifluoromethyl-pyridin-2-yl)-amine (83.76 g, 297 mmol) keeping the internal temperature below 20 °C, stirring was continued at 23 °C for 30 min. Poured onto ice, made alkaline with 32% NaOH-sol. (ca. 800 mL) with external ice cooling, saturated with solid NaCl, extracted twice with THF/TBME/DCM, dried over Na₂SO₄. Removal of the solvent in vacuum left the title compound as a white solid (44.27 g, 92%). MS (ISP) 163.2 [(M+H)⁺].

30 Step 3) 5-Bromo-3-trifluoromethyl-pyridin-2-ylamine CAS-No. [79456-34-1]

To a solution of the above 3-trifluoromethyl-pyridin-2-ylamine (16.21 g, 100 mmol) in acetonitrile (300 mL) at 5 °C was added NBS (17.8 g, 100 mmol) and the mixture was stirred at 23 °C for 1 h. Poured into ice and additional sat. NaHCO₃-sol., extracted with EtOAc, washed with brine, dried over Na₂SO₄. Removal of the solvent in vacuum left a yellow solid, which was filtered through a silica gel and cotton wool column with dichloromethane to give the title compound as a yellow solid (23.71 g, 98%). MS (EI) 240.1 [(M)⁺], 242.0 [(M+2)⁺].

Step 4) 3-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyridin-2-ylamine

A mixture of the above 5-bromo-3-trifluoromethyl-pyridin-2-ylamine (9.90 g, 41.1 mmol), commercially available 4-(trifluoromethyl)benzeneboronic acid CAS-No. [128796-39-4] (8.58 g, 45.2 mmol), 1N aqueous Na₂CO₃-solution (98.6 mL, 98.6 mmol) and Pd(PPh₃)₄ (475 mg, 1 mol%) in DME (205 mL) was refluxed under argon atmosphere for 1 h. Poured into 5% citric acid, extracted with EtOAc, washed the organic layers with sat. NaHCO₃-sol. and brine, dried over Na₂SO₄. Removal of the solvent in vacuum left a grey solid (13.96 g) which was purified by silica gel flash chromatography with heptane/EtOAc 4:1 to 2:1 to give the title compound as a light yellow solid (10.90 g, 87%). MS (ISP) 305 [(M-H)⁻]; mp 168 °C.

Step 5) N,N-Dimethyl-N'-[3-trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyridin-2-yl]-formamidine

A mixture of the above 3-trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyridin-2-ylamine (4.59 g, 15 mmol) and dimethylformamide dimethyl acetal (2.25 mL, 16 mmol) in toluene was refluxed for 1 h. The reaction mixture was evaporated and dried at HV to give the title compound as a light yellow solid (4.21 g, 78%). MS (ISP) 362 [(M+H)⁺]; mp 114 °C.

Step 6) 8-Trifluoromethyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester

A mixture of the above N,N-dimethyl-N'-[3-trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyridin-2-yl]-formamidine (3.61 g, 10.0 mmol) and ethyl bromoacetate (3.32 mL, 30.0 mmol) in DMF (10 mL) was stirred at 120 °C for 4 h. Cooled down to 100 °C, added DIPEA (0.5 mL, 3.0 mmol) and stirred at 23 °C for 2 h. Poured into sat. NaHCO₃-sol., extracted with EtOAc, washed the organic layers with brine, dried over Na₂SO₄.

Removal of the solvent in vacuum left a brown oil (5.01 g) which was purified by silica gel column chromatography with heptane/EtOAc 9:1 to 4:1 to give the title compound as a light yellow solid (2.89 g, 72%). MS (ISP) 403 [(M+H)⁺]; mp 132 °C.

5 Step 7) 8-Trifluoromethyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-*a*]pyridine-3-carboxylic acid

To a solution of the above 8-trifluoromethyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-*a*]pyridine-3-carboxylic acid ethyl ester (3.06 g, 7.61 mmol) in THF (45 mL), MeOH (5 mL) and water (11.3 mL) at 23 °C was added LiOH•H₂O (479 mg, 11.41 mmol) and the mixture was stirred at 23 °C for 3 h. Poured into icewater, adjusted pH with 1 N HCl
10 (about 11.41 mL) to pH 2-3, saturated with solid NaCl, extracted with EtOAc, dried over Na₂SO₄. Removal of the solvent in vacuum left the title compound as a light brown solid (2.87 g, 101%). MS (ISN) 373 [(M-H)⁻]; mp 248 °C (dec.).

Example C.33

6-(4-Chloro-phenyl)-8-methyl-imidazo[1,2-*a*]pyridine-3-carboxylic acid

15 Step 1) 5-(4-Chloro-phenyl)-3-methyl-pyridin-2-ylamine

Prepared as described in example C.32 (step 4) from commercially available 2-amino-5-bromo-3-methyl-pyridine (4 g, 21.4 mmol) and commercially available 4-chlorophenylboronic acid (3.68 g, 23.5 mmol). Obtained as an off-white solid (3.86 g, 83%). MS (EI) 218.1 [(M)⁺]; mp 156°C.

20 Step 2) N'-[5-(4-Chloro-phenyl)-3-methyl-pyridin-2-yl]-N,N-dimethyl-formamidine

Prepared as described in example C.32 (step 5) from 5-(4-chloro-phenyl)-3-methyl-pyridin-2-ylamine (4.8 g, 21.9 mmol). Obtained after crystallization from diethyl ether/hexane as an off-white solid (4.73 g, 79%). MS (ISP) 274.0 [(M+H)⁺]; mp 99°C.

25 Step 3) 6-(4-Chloro-phenyl)-8-methyl-imidazo[1,2-*a*]pyridine-3-carboxylic acid ethyl ester

Prepared as described in example C.32 (step 6) from N'-[5-(4-chloro-phenyl)-3-methyl-pyridin-2-yl]-N,N-dimethyl-formamidine (4.66 g, 17.0 mmol). Obtained as a light grey solid (5.35 g, 99%). MS (EI) 314.1 [(M)⁺]; mp 147°C.

Step 4) 6-(4-Chloro-phenyl)-8-methyl-imidazo[1,2-a]pyridine-3-carboxylic acid

Prepared as described in example C.32 (step 7) from 6-(4-chloro-phenyl)-8-methyl-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester (5.34 g, 17 mmol). Obtained as an off-white solid (3.32 g, 68%). MS (ISN) 285.0 [(M-H)⁻]; mp 228°C.

5

Example C.34

8-Methyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid

Step 1) 3-Methyl-5-(4-trifluoromethyl-phenyl)-pyridin-2-ylamine

Prepared as described in example C.32 (step 4) from commercially available 2-amino-5-bromo-3-methyl-pyridine (4.5 g, 24.1 mmol) and commercially available 4-trifluoromethyl-phenylboronic acid (5.03 g, 26.5 mmol). Obtained as an off-white solid (5.36 g, 88%). MS (ISP) 252.9 [(M+H)⁺]; mp 159°C.

10

Step 2) N,N-Dimethyl-N'-[3-methyl-5-(4-trifluoromethyl-phenyl)-pyridin-2-yl]-formamidine

Prepared as described in example C.32 (step 5) from 3-methyl-5-(4-trifluoromethyl-phenyl)-pyridin-2-ylamine (5.16 g, 20.4 mmol). Obtained as a light yellow solid (6.21 g, 99%). MS (ISP) 308.1 [(M+H)⁺]; mp 74°C.

15

Step 3) 8-Methyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester

Prepared as described in example C.32 (step 6) from N,N-dimethyl-N'-[3-methyl-5-(4-trifluoromethyl-phenyl)-pyridin-2-yl]-formamidine (5.98 g, 19.5 mmol). Obtained as an off-white solid (5.92 g, 87%). MS (EI) 348.1 [(M)⁺]; mp 128°C.

20

Step 4) 8-Methyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid

Prepared as described in example C.32 (step 7) from 8-methyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester (5.78 g, 16.6 mmol). Obtained as an off-white solid (4.53 g, 85%). MS (ISN) 319.1 [(M-H)⁻]; mp 211°C.

25

Example C.35

6-(4-Trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid

Step 1) 5-(4-Trifluoromethyl-phenyl)-pyridin-2-ylamine

Prepared as described in example C.32 (step 4) from commercially available 2-amino-5-bromo-pyridine (3.46 g, 20.0 mmol) and commercially available 4-trifluoromethyl-phenylboronic acid (4.18 g, 22.0 mmol). Obtained as an off-white solid (3.36 g, 71%). Mp
5 130°C.

Step 2) N,N-Dimethyl-N'-[5-(4-trifluoromethyl-phenyl)-pyridin-2-yl]-formamidine

Prepared as described in example C.32 (step 5) from 5-(4-trifluoromethyl-phenyl)-pyridin-2-ylamine (3.35 g, 14.1 mmol). Obtained as a light brown solid (4.08 g, 99%). MS (ISP) 294.2 [(M+H)⁺]; mp 154°C.

10 Step 3) 6-(4-Trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester

Prepared as described in example C.32 (step 6) from N,N-dimethyl-N'-[5-(4-trifluoromethyl-phenyl)-pyridin-2-yl]-formamidine (3.93 g, 13.4 mmol). Obtained as a light brown solid (3.07 g, 69%). MS (EI) 334.1 [(M)⁺]; mp 118°C.

15 Step 4) 6-(4-Trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid

Prepared as described in example C.32 (step 7) from 6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester (2.98 g, 8.91 mmol). Obtained as a white solid (2.21 g, 81%). MS (ISN) 305.1 [(M-H)⁻]; mp 220°C.

Example C.36

20 6-(4-Chloro-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid

Step 1) 5-(4-Chloro-phenyl)-pyridin-2-ylamine

Prepared as described in example C.32 (step 4) from commercially available 2-amino-5-bromo-pyridine (3.46 g, 20.0 mmol) and commercially available 4-chloromethyl-phenylboronic acid (3.44 g, 22.0 mmol). Obtained as a white solid (3.07 g, 75%). MS (EI)
25 204.0 [(M)⁺]; mp 132°C.

Step 2) N,N-Dimethyl-N'-[5-(4-chloro-phenyl)-pyridin-2-yl]-formamidine

- 46 -

Prepared as described in example C.32 (step 5) from 5-(4-chloro-phenyl)-pyridin-2-ylamine (2.92 g, 14.3 mmol). Obtained as a light brown solid (3.68 g, 99%). MS (ISP) 259.9 [(M+H)⁺]; mp 125°C.

Step 3) 6-(4-Chloro-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester

- 5 Prepared as described in example C.32 (step 6) from N,N-dimethyl-N'-[5-(4-chloro-phenyl)-pyridin-2-yl]-formamidine (3.53 g, 13.6 mmol). Obtained as an off-white solid (3.49 g, 85%). MS (EI) 300.1 [(M)⁺]; mp 130°C.

Step 4) 6-(4-Chloro-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid

- 10 Prepared as described in example C.32 (step 7) from 6-(4-chloro-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid ethyl ester (3.45 g, 11.5 mmol). Obtained as a white solid (2.69 g, 86%). MS (ISN) 271.2 [(M-H)⁻]; mp 206°C.

Synthesis of compounds of formula (I) according to the invention

Example 1

- 15 4-{5-[7-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide

- The title compound was prepared from 7-trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.2) (188 mg, 0.5 mmol) and N-hydroxy-4-sulfamoyl-benzamidine [CAS-No. 4476-10-2] (161 mg, 0.75 mmol) according to general procedure II. Obtained after purification by flash chromatography (ethyl acetate/heptane) and crystallization (ethyl acetate/MeOH/hexane) as a light yellow solid (179 mg, 65%). MS (ISN) 552.8 [(M-H)⁻]; mp 275°C.
- 20

Example 2

- 3-{5-[7-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide

The title compound was prepared from 7-trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.2) (188 mg, 0.5 mmol) and N-hydroxy-3-sulfamoyl-benzamidine [CAS-No. 9000-88-7] (161 mg, 0.75 mmol) according to general procedure II. Obtained after purification by column chromatography
5 (dichloromethane/ MeOH/NH₄OH) and crystallization (ethyl acetate/MeOH/hexane) as a yellow solid (175 mg, 63%). MS (ISN) 552.8 [(M-H)⁻]; mp 262°C.

Example 3

3-(3-Pyridin-3-yl-[1,2,4]oxadiazol-5-yl)-7-trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine

10 The title compound was prepared from 7-trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.2) (188 mg, 0.5 mmol) and commercially available N-hydroxy-nicotinamidine [CAS-No. 1594-58-7] (103 mg, 0.75 mmol) according to general procedure II. Obtained after purification by column chromatography (dichloromethane/ MeOH/NH₄OH) and crystallization
15 (dichloromethane/MeOH/hexane) as a yellow solid (126 mg, 53%). MS (EI) 476.1 [(M+H)⁺]; mp 199°C.

Example 4

4-{5-[7-Difluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide

20 The title compound was prepared from 7-difluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.1) (179 mg, 0.5 mmol) and N-hydroxy-4-sulfamoyl-benzamidine [CAS-No. 4476-10-2] (161 mg, 0.75 mmol) according to general procedure II. Obtained after purification by column chromatography (dichloromethane/ MeOH/NH₄OH) and crystallization (ethyl acetate/hexane) as a light
25 yellow solid (159 mg, 59%). MS (ISN) 535.3 [(M-H)⁻]; mp 283°C.

Example 5

3-{5-[7-Difluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide

- 48 -

The title compound was prepared from 7-difluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.1) (179 mg, 0.5 mmol) and N-hydroxy-3-sulfamoyl-benzamidine [CAS-No. 9000-88-7] (161 mg, 0.75 mmol) according to general procedure II. Obtained after purification by column chromatography (dichloromethane/ MeOH/NH₄OH) and crystallization (ethyl acetate/hexane) as a yellow solid (198 mg, 74%). MS (ISN) 535.3 [(M-H)⁻]; mp 267°C.

Example 6

3-{5-[5-(4-Chloro-phenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide

The title compound was prepared from 5-(4-chloro-phenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.28) (157 mg, 0.5 mmol) and N-hydroxy-3-sulfamoyl-benzamidine [CAS-No. 9000-88-7] (161 mg, 0.75 mmol) according to general procedure II. Obtained after purification by column chromatography (dichloromethane/ MeOH/NH₄OH) and crystallization (dichloromethane) as an off-white solid (113 mg, 46%). MS (EI) 492.1 [(M)⁺]; mp 285°C.

Example 7

3-{5-[7-Cyclopropyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide

The title compound was prepared from 7-cyclopropyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.29) (174 mg, 0.5 mmol) and N-hydroxy-3-sulfamoyl-benzamidine [CAS-No. 9000-88-7] (161 mg, 0.75 mmol) according to general procedure II. Obtained after purification by column chromatography (dichloromethane/ MeOH/NH₄OH) and crystallization (ethyl acetate/MeOH/hexane) as an off-white solid (142 mg, 54%). MS (EI) 526.1 [(M)⁺]; mp 277°C.

Example 8

4-{5-[5-(4-Chloro-phenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide

The title compound was prepared from 5-(4-chloro-phenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.28) (157 mg, 0.5 mmol) and N-hydroxy-4-sulfamoyl-benzamidine [CAS-No. 4476-10-2] (161 mg, 0.75 mmol) according to general procedure II. Obtained after purification by column chromatography (dichloromethane/MeOH/NH₄OH) and crystallization (dichloromethane) as a light yellow solid (60 mg, 24%). MS (EI) 492.1 [(M)⁺]; mp 260°C.

Example 9

4-{5-[7-Cyclopropyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide

10 The title compound was prepared from 7-cyclopropyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.29) (174 mg, 0.5 mmol) and N-hydroxy-4-sulfamoyl-benzamidine [CAS-No. 4476-10-2] (161 mg, 0.75 mmol) according to general procedure II. Obtained after purification by column chromatography (dichloromethane/ MeOH/NH₄OH) and crystallization
15 (dichloromethane/MeOH/hexane) as a light yellow solid (191 mg, 73%). MS (EI) 526.1 [(M)⁺]; mp 313°C.

Example 10

3-{5-[5-(4-Chloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide

20 The title compound was prepared from 5-(4-chloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.4) (171 mg, 0.5 mmol) and N-hydroxy-3-sulfamoyl-benzamidine [CAS-No. 9000-88-7] (161 mg, 0.75 mmol) according to general procedure II. Obtained after purification by column chromatography (dichloromethane/ MeOH/NH₄OH) and crystallization (dichloromethane) as a light
25 yellow solid (200 mg, 77%). MS (ISP) 521.2 [(M+H)⁺]; mp 247°C.

Example 11

3-{5-[8-Trifluoromethyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide

The title compound was prepared from 8-trifluoromethyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid (example C.32) (187 mg, 0.5 mmol) and N-hydroxy-3-sulfamoyl-benzamidine [CAS-No. 9000-88-7] (161 mg, 0.75 mmol) according

- 50 -

to general procedure II. Obtained after purification by column chromatography (dichloromethane/ MeOH/NH₄OH) and crystallization (dichloromethane) as an off-white solid (117 mg, 42%). MS (ISN) 552.0 [(M-H)⁻]; mp 297°C.

Example 12

5 4-{5-[5-(4-Chloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-benzenesulfonamide

The title compound was prepared from 5-(4-chloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.4) (171 mg, 0.5 mmol) and N-hydroxy-4-sulfamoyl-benzamidine [CAS-No. 4476-10-2] (161 mg, 0.75 mmol) according to general procedure II. Obtained after purification by flash chromatography (ethyl acetate/heptane) and crystallization (dichloromethane) as a yellow solid (150 mg, 58%). MS (EI) 520.0 [(M)⁺]; mp 296°C.

Example 13

4-{5-[8-Trifluoromethyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-
15 [1,2,4]oxadiazol-3-yl}-benzenesulfonamide

The title compound was prepared from 8-trifluoromethyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-*a*]pyridine-3-carboxylic acid (example C.32) (187 mg, 0.5 mmol) and N-hydroxy-4-sulfamoyl-benzamidine [CAS-No. 4476-10-2] (161 mg, 0.75 mmol) according to general procedure II. Obtained after purification by flash chromatography (ethyl acetate/heptane) and crystallization (dichloromethane) as a yellow solid (143 mg, 52%). MS (EI) 553.1 [(M)⁺]; mp 292°C.

Example 14

4-{3-[7-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-5-yl}-benzenesulfonamide

25 The title compound was prepared from N-hydroxy-7-trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxamide (example B.1) (195 mg, 0.5 mmol) and commercially available 4-sulfamoyl-benzoic acid (101 mg, 0.5 mmol) according to general procedure II. Obtained after purification by flash chromatography (ethyl acetate/heptane) and crystallization (dichloromethane) as a yellow solid (155 mg, 30 56%). MS (ISN) 553.3 [(M-H)⁻]; mp 292°C.

Example 15

3-{3-[7-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-5-yl}-benzenesulfonamide

The title compound was prepared from N-hydroxy-7-trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxamide (example B.1) (195
5 mg, 0.5 mmol) and commercially available 3-sulfamoyl-benzoic acid (101 mg, 0.5 mmol) according to general procedure II. Obtained after purification by flash chromatography (ethyl acetate/heptane) and crystallization (dichloromethane) as a yellow solid (144 mg, 52%). MS (ISN) 553.3 [(M-H)⁻]; mp 285°C.

Example 16

10 3-(5-{5-[3-(2,2,2-Trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl}-[1,2,4]oxadiazol-3-yl)-benzenesulfonamide

The title compound was prepared from 5-[3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.10) (237 mg, 0.5 mmol) and N-hydroxy-3-sulfamoyl-benzamide [CAS-No. 9000-88-7]
15 (161 mg, 0.75 mmol) according to general procedure II. Obtained after purification by flash chromatography (ethyl acetate/hexane) and crystallization (dichloromethane) as a light yellow solid (220 mg, 67%). MS (EI) 652.2 [(M)⁺]; mp 250°C.

Example 17

20 3-{5-[5-(3-Methyl-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide

The title compound was prepared from 5-(3-methyl-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.8) (195 mg, 0.5 mmol) and N-hydroxy-3-sulfamoyl-benzamide [CAS-No. 9000-88-7] (161 mg, 0.75 mmol) according to general procedure II. Obtained after purification by flash
25 chromatography (ethyl acetate/heptane) and crystallization (dichloromethane) as a light yellow solid (190 mg, 67%). MS (EI) 568.1 [(M)⁺]; mp 270°C.

Example 18

4-{5-[5-(3-Methyl-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide

The title compound was prepared from 5-(3-methyl-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.8) (195 mg, 0.5 mmol) and N-hydroxy-4-sulfamoyl-benzamidine [CAS-No. 4476-10-2] (161 mg, 0.75 mmol) according to general procedure II. Obtained after purification by flash chromatography (ethyl acetate/heptane) and crystallization (dichloromethane) as a yellow solid (200 mg, 70%). MS (ISN) 567.2 [(M-H)⁻]; mp 273°C.

Example 19

3-{5-[5-(4-Chloro-phenyl)-7-difluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide

The title compound was prepared from 5-(4-chloro-phenyl)-7-difluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.3) (162 mg, 0.5 mmol) and N-hydroxy-3-sulfamoyl-benzamidine [CAS-No. 9000-88-7] (161 mg, 0.75 mmol) according to general procedure II. Obtained after trituration with water and further purification by crystallization (dichloromethane) as a light yellow solid (170 mg, 68%). MS (ISN) 501.1 [(M-H)⁻]; mp 231°C.

Example 20

5-{5-[5-(4-Chloro-phenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide

The title compound was prepared from 5-(4-chloro-phenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.28) (157 mg, 0.5 mmol) and N-hydroxy-5-sulfamoyl-thiophene-2-carboxamide (example B.2) (166 mg, 0.75 mmol) according to general procedure II. Obtained after purification by flash chromatography (ethyl acetate/heptane) and crystallization (ethyl acetate/dichloromethane) as a light brown solid (130 mg, 52%). MS (EI) 498.1 [(M)⁺]; mp 294°C.

Example 21

4-{3-[4-Trifluoromethyl-2-(4-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidin-8-yl]-[1,2,4]oxadiazol-5-yl}-benzenesulfonamide

The title compound was prepared from N-hydroxy-4-trifluoromethyl-2-(4-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidine-8-carboxamide (example B.3) (195 mg, 0.5 mmol) and commercially available 4-sulfamoyl-benzoic acid (101 mg, 0.5 mmol) according to general procedure II. Obtained after purification by column

chromatography (dichloromethane/ MeOH/NH₄OH) and crystallization (dichloromethane) as a yellow solid (61 mg, 22%). MS (ISP) 555.3 [(M+H)⁺]; mp 303°C.

Example 22

5 5-{5-[5-(3-Methyl-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide
The title compound was prepared from 5-(3-methyl-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.8) (195 mg, 0.5 mmol) and N-hydroxy-5-sulfamoyl-thiophene-2-carboxamide (example B.2) (166 mg, 0.75 mmol) according to general procedure II. Obtained after purification by flash
10 chromatography (ethyl acetate/heptane) and crystallization (dichloromethane) as a light yellow solid (50 mg, 17%). MS (ISN) 573.2 [(M-H)⁻]; mp 324°C.

Example 23

5-(5-{5-[3-(2,2,2-Trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl}-[1,2,4]oxadiazol-3-yl)-thiophene-2-sulfonic acid amide
15 The title compound was prepared from 5-[3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.10) (237 mg, 0.5 mmol) and N-hydroxy-5-sulfamoyl-thiophene-2-carboxamide (example B.2) (166 mg, 0.75 mmol) according to general procedure II. Obtained after purification by flash chromatography (ethyl acetate/hexane) and crystallization (dichloromethane) as
20 a yellow solid (220 mg, 67%). MS (ISP) 659.3 [(M+H)⁺]; mp 255°C.

Example 24

5-{5-[7-Cyclopropyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide
The title compound was prepared from 7-cyclopropyl-5-(4-trifluoromethyl-phenyl)-
25 pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.29) (174 mg, 0.5 mmol) N-hydroxy-5-sulfamoyl-thiophene-2-carboxamide (example B.2) (166 mg, 0.75 mmol) and according to general procedure II. Obtained after purification by flash chromatography (ethyl acetate/heptane) and crystallization (dichloromethane/ethyl acetate) as a yellow solid (180 mg, 68%). MS (ISP) 533.3 [(M+H)⁺]; mp 290°C.

4-{5-[7-Trifluoromethyl-5-(3-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-benzenesulfonamide

The title compound was prepared from 7-trifluoromethyl-5-(3-trifluoromethyl-phenyl)-
pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.31) (188 mg, 0.5 mmol) and N-
5 hydroxy-4-sulfamoyl-benzamidine [CAS-No. 4476-10-2] (161 mg, 0.75 mmol) according
to general procedure II. Obtained after purification by flash chromatography (ethyl
acetate/heptane) and crystallization (ethyl acetate/dichloromethane) as a yellow solid
(220 mg, 79%). MS (ISP) 555.3 [(M+H)⁺]; mp 300°C.

Example 26

10 3-{5-[7-Trifluoromethyl-5-(3-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-benzenesulfonamide

The title compound was prepared from 7-trifluoromethyl-5-(3-trifluoromethyl-phenyl)-
pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.31) (188 mg, 0.5 mmol) and N-
hydroxy-3-sulfamoyl-benzamidine [CAS-No. 9000-88-7] (161 mg, 0.75 mmol) according
15 to general procedure II. Obtained after purification by flash chromatography (ethyl
acetate/heptane) and crystallization (dichloromethane) as a light yellow solid (120 mg,
43%). MS (ISN) 552.9 [(M-H)⁻]; mp 251°C.

Example 27

20 5-{5-[7-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide

The title compound was prepared from 7-trifluoromethyl-5-(4-trifluoromethyl-phenyl)-
pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.2) (188 mg, 0.5 mmol) and N-
hydroxy-5-sulfamoyl-thiophene-2-carboxamidine (example B.2) (166 mg, 0.75 mmol)
according to general procedure II. Obtained after purification by flash chromatography
25 (ethyl acetate/heptane) and crystallization (dichloromethane) as an off-white solid (130
mg, 46%). MS (ISN) 558.0 [(M-H)⁻]; mp 276°C.

Example 28

5-{5-[5-(4-Chloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide

The title compound was prepared from 5-(4-chloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.4) (171 mg, 0.5 mmol) and N-hydroxy-5-sulfamoyl-thiophene-2-carboxamide (example B.2) (166 mg, 0.75 mmol) according to general procedure II. Obtained after purification by flash chromatography (ethyl acetate/heptane) and crystallization (dichloromethane) as a yellow solid (180 mg, 68%). MS (ISN) 525.0 [(M-H)⁻]; mp 294°C.

Example 29

5-{5-[5-(4-Chloro-phenyl)-7-difluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide

10 The title compound was prepared from 5-(4-chloro-phenyl)-7-difluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.3) (162 mg, 0.5 mmol) and N-hydroxy-5-sulfamoyl-thiophene-2-carboxamide (example B.2) (166 mg, 0.75 mmol) according to general procedure II. Obtained after purification by flash chromatography (ethyl acetate/heptane) and crystallization (dichloromethane) as a light yellow solid (96 mg, 38%). MS (EI) 508.0 [(M)⁺]; mp 259°C.

Example 30

5-{5-[7-Methyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide

The title compound was prepared from 7-methyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.25) (161 mg, 0.5 mmol) and N-hydroxy-5-sulfamoyl-thiophene-2-carboxamide (example B.2) (166 mg, 0.75 mmol) according to general procedure II. Obtained after purification by column chromatography (dichloromethane/ MeOH/NH₄OH) and crystallization (dichloromethane/MeOH) as a light yellow solid (88 mg, 35%). MS (EI) 506.1 [(M+H)⁺]; mp 276°C.

Example 31

5-{5-[7-Difluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide

The title compound was prepared from 7-difluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.1) (179 mg, 0.5 mmol) and N-hydroxy-5-sulfamoyl-thiophene-2-carboxamide (example B.2) (166 mg, 0.75 mmol)

- 56 -

according to general procedure II. Obtained after purification by flash chromatography (ethyl acetate/heptane) and crystallization (dichloromethane) as a yellow solid (200 mg, 74%). MS (EI) 542.0 [(M+H)⁺]; mp 278°C.

Example 32

5 5-{5-[5-(4-Chloro-phenyl)-7-methyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide

The title compound was prepared from 5-(4-chloro-phenyl)-7-methyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.24) (144 mg, 0.5 mmol) and N-hydroxy-5-sulfamoyl-thiophene-2-carboxamide (example B.2) (166 mg, 0.75 mmol) according to
10 general procedure II. Obtained after purification by column chromatography (dichloromethane/ MeOH/NH₄OH)) and crystallization (MeOH/dichloromethane) as a light yellow solid (79 mg, 33%). MS (ISP) 473.3 [(M+H)⁺]; mp 253°C.

Example 33

15 5-{3-[7-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-5-yl}-thiophene-2-sulfonic acid amide

The title compound was prepared from N-hydroxy-4-trifluoromethyl-2-(4-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidine-8-carboxamide (example B.3) (195 mg, 0.5 mmol) and commercially available 2-sulfamoyl-thiophene-5-carboxylic acid [CAS-No. 7353-87-9] (104 mg, 0.5 mmol) according to general procedure II. Obtained
20 after purification by flash chromatography (ethyl acetate/heptane) and crystallization (dichloromethane) as a yellow solid (110 mg, 39%). MS (EI) 560.0 [(M)⁺]; mp 272°C.

Example 34

25 5-{5-[7-Trifluoromethyl-5-(3-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine

The title compound was prepared from 7-trifluoromethyl-5-(3-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.31) (188 mg, 0.5 mmol) and 6-amino-N-hydroxy-nicotinamide (example B.4) (114 mg, 0.75 mmol) according to general procedure II. Obtained after purification by flash chromatography (ethyl acetate/heptane) and crystallization (dichloromethane/hexane) as a yellow solid (22 mg,
30 9%). MS (ISP) 492.1 [(M+H)⁺]; mp 264°C.

Example 35

5- $\{5-[7\text{-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}\}$ -pyridin-2-ylamine

The title compound was prepared from 7-trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.2) (188 mg, 0.5 mmol) and 6-amino-N-hydroxy-nicotinamidine (example B.4) (114 mg, 0.75 mmol) according to general procedure II. Obtained after purification by flash chromatography (ethyl acetate/heptane) and crystallization (dichloromethane/hexane) as a yellow solid (85 mg, 35%). MS (ISP) 492.1 [(M+H)⁺]; mp 257°C.

Example 36

10 5- $\{5-[7\text{-Difluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}\}$ -pyridin-2-ylamine

The title compound was prepared from 7-difluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.1) (179 mg, 0.5 mmol) and 6-amino-N-hydroxy-nicotinamidine (example B.4) (114 mg, 0.75 mmol) according to general procedure II. Obtained after purification by flash chromatography (ethyl acetate/heptane) and crystallization (ethyl acetate/hexane) as a yellow solid (84 mg, 35%). MS (ISP) 474.0 [(M+H)⁺]; mp 242°C.

Example 37

20 5- $\{5-[5\text{-(3-Methyl-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl}]-[1,2,4]oxadiazol-3-yl}\}$ -pyridin-2-ylamine

The title compound was prepared from 5-(3-methyl-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.8) (195 mg, 0.5 mmol) and 6-amino-N-hydroxy-nicotinamidine (example B.4) (114 mg, 0.75 mmol) according to general procedure II. Obtained after purification by flash chromatography (ethyl acetate/heptane) and crystallization (dichloromethane/hexane) as a yellow solid (98 mg, 39%). MS (ISP) 506.2 [(M+H)⁺]; mp 220°C.

Example 38

3- $\{5-[5\text{-(4-Chloro-phenyl)-7-methyl-pyrazolo[1,5-a]pyrimidin-3-yl}]-[1,2,4]oxadiazol-3-yl}\}$ -benzenesulfonamide

30 The title compound was prepared from 5-(4-chloro-phenyl)-7-methyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.24) (144 mg, 0.5 mmol) and N-hydroxy-3-

sulfamoyl-benzamidine [CAS-No. 9000-88-7] (161 mg, 0.75 mmol) according to general procedure II. Obtained after purification by flash chromatography (ethyl acetate/heptane) and crystallization (MeOH/dichloromethane) as a light yellow solid (70 mg, 30%). MS (EI) 466.1 [(M)⁺]; mp 275°C.

5

Example 39

4-{5-[6-(4-Chloro-phenyl)-8-methyl-imidazo[1,2-a]pyridin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide

The title compound was prepared from 6-(4-chloro-phenyl)-8-methyl-imidazo[1,2-a]pyridine-3-carboxylic acid (example C.33) (143 mg, 0.5 mmol) and N-hydroxy-4-sulfamoyl-benzamidine [CAS-No. 4476-10-2] (161 mg, 0.75 mmol) according to general procedure II. Obtained after purification by flash chromatography (ethyl acetate/heptane) and crystallization (MeOH) as an off-white solid (143 mg, 61%). MS (EI) 465.1 [(M)⁺]; mp 311°C.

Example 40

15 3-{5-[6-(4-Chloro-phenyl)-8-methyl-imidazo[1,2-a]pyridin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide

The title compound was prepared from 6-(4-chloro-phenyl)-8-methyl-imidazo[1,2-a]pyridine-3-carboxylic acid (example C.33) (143 mg, 0.5 mmol) and N-hydroxy-3-sulfamoyl-benzamidine [CAS-No. 9000-88-7] (161 mg, 0.75 mmol) according to general procedure II. Obtained after trituration with water and further purification by crystallization (MeOH/diethyl ether) as an off-white solid (152 mg, 65%). MS (EI) 465.1 [(M)⁺]; mp 301°C.

Example 41

25 5-{5-[6-(4-Chloro-phenyl)-8-methyl-imidazo[1,2-a]pyridin-3-yl]-[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide

The title compound was prepared from 6-(4-chloro-phenyl)-8-methyl-imidazo[1,2-a]pyridine-3-carboxylic acid (example C.33) (143 mg, 0.5 mmol) and N-hydroxy-5-sulfamoyl-thiophene-2-carboxamide (example B.2) (166 mg, 0.75 mmol) according to general procedure II. Obtained after trituration with water and further purification by crystallization (MeOH/diethyl ether) as an off-white solid (159 mg, 67%). MS (ISN) 470.0 [(M-H)⁻]; mp 271°C.

30

Example 42

5- $\{5-[4\text{-Trifluoromethyl-2-(4-trifluoromethyl-phenyl)-imidazo}[1,5\text{-a}]\text{pyrimidin-8-yl}-[1,2,4]\text{oxadiazol-3-yl}\}$ -thiophene-2-sulfonic acid amide

The title compound was prepared from 4-trifluoromethyl-2-(4-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidine-8-carboxylic acid (example C.30) (188 mg, 0.5 mmol) and N-hydroxy-5-sulfamoyl-thiophene-2-carboxamide (example B.2) (166 mg, 0.75 mmol) according to general procedure II. Obtained after purification by flash chromatography (ethyl acetate/heptane) and crystallization (dichloromethane/ethyl acetate) as a yellow solid (199 mg, 71%). MS (ISP) 559.1 [(M-H)⁻]; mp 295°C.

10

Example 43

4- $\{5-[8\text{-Methyl-6-(4-trifluoromethyl-phenyl)-imidazo}[1,2\text{-a}]\text{pyridin-3-yl}-[1,2,4]\text{oxadiazol-3-yl}\}$ -benzenesulfonamide

The title compound was prepared from 8-methyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid (example C.34) (160 mg, 0.5 mmol) and N-hydroxy-4-sulfamoyl-benzamide [CAS-No. 4476-10-2] (161 mg, 0.75 mmol) according to general procedure II. Obtained after trituration with water and further purification by crystallization (MeOH/diethyl ether) as an off-white solid (146 mg, 58%). MS (ISP) 500.3 [(M+H)⁺]; mp 290°C.

15

Example 44

3- $\{5-[8\text{-Methyl-6-(4-trifluoromethyl-phenyl)-imidazo}[1,2\text{-a}]\text{pyridin-3-yl}-[1,2,4]\text{oxadiazol-3-yl}\}$ -benzenesulfonamide

The title compound was prepared from 8-methyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid (example C.34) (160 mg, 0.5 mmol) and N-hydroxy-3-sulfamoyl-benzamide [CAS-No. 9000-88-7] (161 mg, 0.75 mmol) according to general procedure II. Obtained after trituration with water and further purification by crystallization (MeOH/diethyl ether) as an off-white solid (175 mg, 70%). MS (ISP) 500.3 [(M+H)⁺]; mp 326°C.

20

Example 45

5- $\{5-[8\text{-Methyl-6-(4-trifluoromethyl-phenyl)-imidazo}[1,2\text{-a}]\text{pyridin-3-yl}-[1,2,4]\text{oxadiazol-3-yl}\}$ -thiophene-2-sulfonic acid amide

25

30

- 60 -

The title compound was prepared from 8-methyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid (example C.34) (160 mg, 0.5 mmol) and N-hydroxy-5-sulfamoyl-thiophene-2-carboxamide (example B.2) (166 mg, 0.75 mmol) according to general procedure II. Obtained after purification by column chromatography (dichloromethane/ MeOH/NH₄OH) and crystallization (diethyl ether/MeOH) as a pink solid (147 mg, 58%). MS (EI) 505.1 [(M)⁺]; mp 285°C.

Example 46

5- $\{5-[7\text{-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}\}$ -pyrimidin-2-ylamine

10 The title compound was prepared from 7-trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.2) (188 mg, 0.5 mmol) 2-amino-N-hydroxy-pyrimidine-5-carboxamide (example B.5) (115 mg, 0.75 mmol) according to general procedure II. Obtained after purification by flash chromatography (ethyl acetate/heptane) and crystallization (dichloromethane/MeOH) as a yellow solid
15 (160 mg, 65%). MS (ISP) 493.3 [(M+H)⁺]; mp 254°C.

Example 47

5- $\{5-[8\text{-Methyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-[1,2,4]oxadiazol-3-yl}\}$ -pyridin-2-ylamine

The title compound was prepared from 8-methyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid (example C.34) (160 mg, 0.5 mmol) and 6-amino-N-hydroxy-nicotinamide (example B.4) (114 mg, 0.75 mmol) according to general procedure II. Obtained after purification by column chromatography (dichloromethane/ MeOH/NH₄OH) and crystallization (diethyl ether) as a white solid
20 (32 mg, 15%). MS (EI) 436.1 [(M)⁺]; mp 257°C.

25

Example 48

5- $\{5-[8\text{-Methyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-[1,2,4]oxadiazol-3-yl}\}$ -pyrimidin-2-ylamine

The title compound was prepared from 8-methyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid (example C.34) (160 mg, 0.5 mmol) 2-amino-N-hydroxy-pyrimidine-5-carboxamide (example B.5) (115 mg, 0.75 mmol) according to general procedure II. Obtained after purification by flash chromatography (ethyl
30

- 61 -

acetate/heptane) and crystallization (dichloromethane/hexane) as a white solid (60 mg, 27%). MS (ISP) 438.3 [(M+H)⁺]; mp 302°C.

Example 49

3-{5-[5-(4-Chloro-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-
5 benzenesulfonamide

The title compound was prepared from 5-(4-chloro-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.22) (137 mg, 0.5 mmol) and N-hydroxy-3-sulfamoyl-benzamidine [CAS-No. 9000-88-7] (161 mg, 0.75 mmol) according to general procedure II. Obtained after purification by flash chromatography (dichloromethane/ MeOH) and
10 crystallization (dichloromethane) as an off-white solid (86 mg, 38%). MS (ISN) 451.2 [(M-H)⁻]; mp 223°C.

Example 50

4-{5-[6-(4-Trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-[1,2,4]oxadiazol-3-yl}-
benzenesulfonamide
15 The title compound was prepared from 6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid (example C.35) (153 mg, 0.5 mmol) and N-hydroxy-4-sulfamoyl-benzamidine [CAS-No. 4476-10-2] (161 mg, 0.75 mmol) according to general procedure II. Obtained after trituration with water and further purification by crystallization (heptane/diethyl ether) as an off-white solid (186 mg, 77%). MS (ISP)
20 486.3 [(M+H)⁺]; mp 288°C.

Example 51

3-{5-[6-(4-Trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-[1,2,4]oxadiazol-3-yl}-
benzenesulfonamide
The title compound was prepared from 6-(4-trifluoromethyl-phenyl)-imidazo[1,2-
25 a]pyridine-3-carboxylic acid (example C.35) (153 mg, 0.5 mmol) and N-hydroxy-3-sulfamoyl-benzamidine [CAS-No. 9000-88-7] (161 mg, 0.75 mmol) according to general procedure II. Obtained after trituration with water and further purification by crystallization (MeOH/diethyl ether) as an off-white solid (202 mg, 83%). MS (ISP) 486.3 [(M+H)⁺]; mp 288°C.

30

Example 52

5- $\{5-[5-(4\text{-Trifluoromethyl-phenyl})\text{-pyrazolo}[1,5\text{-a}]\text{pyrimidin-3-yl}]-[1,2,4]\text{oxadiazol-3-yl}\}$ -thiophene-2-sulfonic acid amide

The title compound was prepared from 6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid (example C.23) (154 mg, 0.5 mmol) and N-hydroxy-5-sulfamoyl-thiophene-2-carboxamide (example B.2) (166 mg, 0.75 mmol) according to general procedure II. Obtained after purification by flash chromatography (dichloromethane/ MeOH) and crystallization (dichloromethane) as a yellow solid (154 mg, 62%). MS (ISP) 493.0 [(M+H)⁺]; mp 251°C.

Example 53

10 3- $\{5-[5-(4\text{-Trifluoromethyl-phenyl})\text{-pyrazolo}[1,5\text{-a}]\text{pyrimidin-3-yl}]-[1,2,4]\text{oxadiazol-3-yl}\}$ -benzenesulfonamide

The title compound was prepared from 6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid (example C.23) (154 mg, 0.5 mmol) and N-hydroxy-3-sulfamoyl-benzamide [CAS-No. 9000-88-7] (161 mg, 0.75 mmol) according to general procedure II. Obtained after purification by flash chromatography (dichloromethane/ MeOH) and crystallization (dichloromethane) as a yellow solid (96 mg, 39%). MS (ISP) 487.1 [(M+H)⁺]; mp 270°C.

Example 54

20 5- $\{5-[6-(4\text{-Trifluoromethyl-phenyl})\text{-imidazo}[1,2\text{-a}]\text{pyridin-3-yl}]-[1,2,4]\text{oxadiazol-3-yl}\}$ -thiophene-2-sulfonic acid amide

The title compound was prepared from 6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid (example C.35) (153 mg, 0.5 mmol) and N-hydroxy-5-sulfamoyl-thiophene-2-carboxamide (example B.2) (166 mg, 0.75 mmol) according to general procedure II. Obtained after trituration with water and further purification by crystallization (heptane/diethyl ether) as an off-white solid (179 mg, 83%). MS (ISP) 492.2 [(M+H)⁺]; mp 280°C.

Example 55

5- $\{5-[6-(4\text{-Chloro-phenyl})\text{-imidazo}[1,2\text{-a}]\text{pyridin-3-yl}]-[1,2,4]\text{oxadiazol-3-yl}\}$ -thiophene-2-sulfonic acid amide

- 63 -

The title compound was prepared from 6-(4-chloro-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid (example C.36) (136 mg, 0.5 mmol) and N-hydroxy-5-sulfamoyl-thiophene-2-carboxamidine (example B.2) (166 mg, 0.75 mmol) according to general procedure II. Obtained after trituration with water and further purification by
5 crystallization (heptane/diethyl ether) as an off-white solid (160 mg, 70%). MS (ISP) 458.2 [(M+H)⁺]; mp 263°C.

Example 56

5-{5-[6-(4-Trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine

10 The title compound was prepared from 6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid (example C.35) (153 mg, 0.5 mmol) and 6-amino-N-hydroxy-nicotinamidine (example B.4) (114 mg, 0.75 mmol) according to general procedure II. Obtained after flash chromatography on silica gel (ethyl acetate) and further purification by crystallization (MeOH/diethyl ether) as a white solid (27 mg, 13%). MS
15 (ISP) 423.3 [(M+H)⁺]; mp 258°C.

Example 57

5-{5-[6-(4-Chloro-phenyl)-imidazo[1,2-a]pyridin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine

The title compound was prepared from 6-(4-chloro-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid (example C.36) (136 mg, 0.5 mmol) and 6-amino-N-hydroxy-nicotinamidine (example B.4) (114 mg, 0.75 mmol) according to general procedure II. Obtained after flash chromatography on silica gel (ethyl acetate) and further purification by crystallization (MeOH/diethyl ether) as a white solid (34 mg, 17%). MS (ISP) 389.3 [(M+H)⁺]; mp 273°C.

25

Example 58

4-{5-[7-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine

The title compound was prepared from 7-trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.2) (188 mg, 0.5 mmol) and 2-amino-N-hydroxy-pyridine-4-carboxamidine (example B.6) (114 mg, 0.75 mmol)
30

according to general procedure II. Obtained after purification by flash chromatography on silica gel (ethyl acetate/heptane) and crystallization (dichloromethane/hexane) as a yellow solid (162 mg, 66%). MS (ISP) 492.1 [(M+H)⁺]; mp 277°C.

Example 59

5 4-{5-[5-(4-Trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine

The title compound was prepared from 6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid (example C.23) (154 mg, 0.5 mmol) and 2-amino-N-hydroxy-pyridine-4-carboxamide (example B.6) (114 mg, 0.75 mmol) according to
10 general procedure II. Obtained after purification by flash chromatography on silica gel (ethyl acetate/heptane) and crystallization (MeOH/dichloromethane/hexane) as a light yellow solid (130 mg, 61%). MS (EI) 423.1 [(M)⁺]; mp 250°C.

Example 60

15 4-{5-[8-Methyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine

The title compound was prepared from 8-methyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid (example C.34) (160 mg, 0.5 mmol) and 2-amino-N-hydroxy-pyridine-4-carboxamide (example B.6) (114 mg, 0.75 mmol) according to general procedure II. Obtained after purification by flash chromatography
20 on silica gel (ethyl acetate/heptane) and crystallization (MeOH/dichloromethane/hexane) as an off-white solid (140 mg, 64%). MS (EI) 436.1 [(M)⁺]; mp 264°C.

Example 61

4-{5-[6-(4-Trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine

25 The title compound was prepared from 6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridine-3-carboxylic acid (example C.35) (153 mg, 0.5 mmol) and 2-amino-N-hydroxy-pyridine-4-carboxamide (example B.6) (114 mg, 0.75 mmol) according to general procedure II. Obtained after purification by column chromatography on silica gel (dichloromethane/MeOH 16:1) and crystallization (MeOH/dichloromethane/hexane) as
30 an off-white solid (80 mg, 38%). MS (EI) 422.9 [(M)⁺]; mp 280°C.

- 65 -

Example 62

5-{5-[5-(4-Chloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine

The title compound was prepared from 5-(4-chloro-phenyl)-7-trifluoromethyl-
5 pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.4) (171 mg, 0.5 mmol) and 6-
amino-N-hydroxy-nicotinamidine (example B.4) (114 mg, 0.75 mmol) according to
general procedure II. Obtained after flash chromatography on silica gel (ethyl
acetate/heptane) and further purification by crystallization (dichloromethane/hexane) as
a yellow solid (81 mg, 36%). MS (ISP) 458.1 [(M+H)⁺]; mp 253°C.

10

Example 63

5-{5-[5-(4-Chloro-phenyl)-7-difluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine

The title compound was prepared from 5-(4-chloro-phenyl)-7-difluoromethyl-
pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.3) (162 mg, 0.5 mmol) and 6-
15 amino-N-hydroxy-nicotinamidine (example B.4) (114 mg, 0.75 mmol) according to
general procedure II. Obtained after flash chromatography on silica gel (ethyl
acetate/heptane) and further purification by crystallization (dichloromethane/hexane) as
a yellow solid (114 mg, 52%). MS (ISP) 440.2 [(M+H)⁺]; mp 254°C.

Example 64

20 5-{5-[5-(4-Chloro-3-methyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine

The title compound was prepared from 5-(4-chloro-3-methyl-phenyl)-7-trifluoromethyl-
pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.6) (178 mg, 0.5 mmol) and 6-
amino-N-hydroxy-nicotinamidine (example B.4) (114 mg, 0.75 mmol) according to
25 general procedure II. Obtained after flash chromatography on silica gel (ethyl
acetate/heptane) and further purification by crystallization (dichloromethane/hexane) as
a yellow solid (66 mg, 28%). MS (ISP) 471.9 [(M+H)⁺]; mp 262°C.

Example 65

- 66 -

5-{5-[7-Difluoromethyl-5-(3-methyl-4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine

The title compound was prepared from 7-difluoromethyl-5-(3-methyl-4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.5) (186 mg, 0.5 mmol) and 6-amino-N-hydroxy-nicotinamidine (example B.4) (114 mg, 0.75 mmol) according to general procedure II. Obtained after flash chromatography on silica gel (ethyl acetate/heptane) and further purification by crystallization (dichloromethane/hexane) as a yellow solid (113 mg, 46%). MS (ISP) 488.1 [(M+H)⁺]; mp 231°C.

Example 66

5-{5-[5-(3,4-Dichloro-phenyl)-7-difluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine

The title compound was prepared from 5-(3,4-dichloro-phenyl)-7-difluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.7) (179 mg, 0.5 mmol) and 6-amino-N-hydroxy-nicotinamidine (example B.4) (114 mg, 0.75 mmol) according to general procedure II. Obtained after flash chromatography on silica gel (ethyl acetate/heptane) and further purification by crystallization (dichloromethane/hexane) as a yellow solid (92 mg, 39%). MS (ISP) 473.9 [(M+H)⁺]; mp 279°C.

Example 67

5-{5-[5-(3,4-Dichloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine

The title compound was prepared from 5-(3,4-dichloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.9) (188 mg, 0.5 mmol) and 6-amino-N-hydroxy-nicotinamidine (example B.4) (114 mg, 0.75 mmol) according to general procedure II. Obtained after flash chromatography on silica gel (ethyl acetate/heptane) and further purification by crystallization (dichloromethane/hexane) as a yellow solid (35 mg, 14%). MS (ISP) 492.0 [(M+H)⁺]; mp 289°C.

Example 68

5-{5-[7-Difluoromethyl-5-(3-ethoxy-4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine

The title compound was prepared from 7-difluoromethyl-5-(3-ethoxy-4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.12) (201 mg, 0.5 mmol) and 6-amino-N-hydroxy-nicotinamidine (example B.4) (114 mg, 0.75 mmol) according to general procedure II. Obtained after flash chromatography on silica gel (ethyl acetate/heptane) and further purification by crystallization (dichloromethane/hexane) as a yellow solid (110 mg, 43%). MS (ISP) 518.1 [(M+H)⁺]; mp 250°C.

Example 69

5-{5-[5-(3-Ethoxy-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine

The title compound was prepared from 5-(3-ethoxy-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.11) (210 mg, 0.5 mmol) and 6-amino-N-hydroxy-nicotinamidine (example B.4) (114 mg, 0.75 mmol) according to general procedure II. Obtained after flash chromatography on silica gel (ethyl acetate/heptane) and further purification by crystallization (dichloromethane/hexane) as a yellow solid (120 mg, 45%). MS (ISP) 536.3 [(M+H)⁺]; mp 263°C.

Example 70

5-(5-{5-[3-(2,2,2-Trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl)-pyridin-2-ylamine

The title compound was prepared from 5-[3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.10) (237 mg, 0.5 mmol) and 6-amino-N-hydroxy-nicotinamidine (example B.4) (114 mg, 0.75 mmol) according to general procedure II. Obtained after flash chromatography on silica gel (ethyl acetate/heptane) and further purification by crystallization (dichloromethane/hexane) as a yellow solid (129 mg, 44%). MS (ISP) 590.3 [(M+H)⁺]; mp 284°C.

Example 71

5-(5-{7-Difluoromethyl-5-[3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl)-pyridin-2-ylamine

The title compound was prepared from 7-difluoromethyl-5-[3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.14) (228 mg, 0.5 mmol) and 6-amino-N-hydroxy-nicotinamidinium (example B.4) (114 mg, 0.75 mmol) according to general procedure II. Obtained after flash chromatography on silica gel (ethyl acetate/heptane) and further purification by crystallization (dichloromethane/hexane) as a yellow solid (125 mg, 44%). MS (ISP) 572.1 [(M+H)⁺]; mp 285°C.

Example 72

5-{5-[5-(3-Chloro-4-trifluoromethyl-phenyl)-7-difluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine

The title compound was prepared from 5-(3-chloro-4-trifluoromethyl-phenyl)-7-difluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.15) (196 mg, 0.5 mmol) and 6-amino-N-hydroxy-nicotinamidinium (example B.4) (114 mg, 0.75 mmol) according to general procedure II. Obtained after flash chromatography on silica gel (ethyl acetate/heptane) and further purification by crystallization (dichloromethane/hexane) as a yellow solid (97 mg, 38%). MS (ISP) 508.2 [(M+H)⁺]; mp 252°C.

Example 73

5-{5-[5-(3-Chloro-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine

The title compound was prepared from 5-(3-chloro-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.17) (205 mg, 0.5 mmol) and 6-amino-N-hydroxy-nicotinamidinium (example B.4) (114 mg, 0.75 mmol) according to general procedure II. Obtained after flash chromatography on silica gel (ethyl acetate/heptane) and further purification by crystallization (dichloromethane/hexane) as a yellow solid (90 mg, 34%). MS (ISP) 526.1 [(M+H)⁺]; mp 234°C.

Example 74

5-{5-[7-Difluoromethyl-5-(3-fluoro-4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine

The title compound was prepared from 7-difluoromethyl-5-(3-fluoro-4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.16) (188 mg, 0.5 mmol) and 6-amino-N-hydroxy-nicotinamidinium (example B.4) (114 mg, 0.75 mmol) according to general procedure II. Obtained after flash chromatography on silica gel (ethyl acetate/heptane) and further purification by crystallization (dichloromethane/hexane) as a yellow solid (86 mg, 35%). MS (EI) 491.1 [(M)⁺]; mp 242°C.

Example 75

5-{5-[5-(3-Fluoro-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine

The title compound was prepared from 5-(3-fluoro-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.18) (197 mg, 0.5 mmol) and 6-amino-N-hydroxy-nicotinamidinium (example B.4) (114 mg, 0.75 mmol) according to general procedure II. Obtained after flash chromatography on silica gel (ethyl acetate/heptane) and further purification by crystallization (dichloromethane/hexane) as a yellow solid (95 mg, 37%). MS (ISP) 510.3 [(M+H)⁺]; mp 233°C.

Example 76

5-{5-[5-(3,4-Difluoro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine

The title compound was prepared from 5-(3,4-difluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.21) (172 mg, 0.5 mmol) and 6-amino-N-hydroxy-nicotinamidinium (example B.4) (114 mg, 0.75 mmol) according to general procedure II. Obtained after flash chromatography on silica gel (ethyl acetate/heptane) and further purification by crystallization (dichloromethane/hexane) as a yellow solid (97 mg, 42%). MS (EI) 459.1 [(M)⁺]; mp 262°C.

Example 77

5-{5-[5-(4-Chloro-3-methyl-phenyl)-7-difluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine

- 70 -

The title compound was prepared from 5-(4-chloro-3-methyl-phenyl)-7-difluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.13) (169 mg, 0.5 mmol) and 6-amino-N-hydroxy-nicotinamide (example B.4) (114 mg, 0.75 mmol) according to general procedure II. Obtained after flash chromatography on silica gel (ethyl acetate/heptane) and further purification by crystallization (dichloromethane/hexane) as a yellow solid (68 mg, 30%). MS (EI) 453.0 [(M)⁺]; mp 243°C.

Example 78

5-{5-[5-(3,4-Difluoro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyrimidin-2-ylamine

The title compound was prepared from 5-(3,4-difluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.21) (172 mg, 0.5 mmol) and 2-amino-N-hydroxy-pyrimidine-5-carboxamide (example B.5) (115 mg, 0.75 mmol) according to general procedure II. Obtained after flash chromatography on silica gel (ethyl acetate/heptane) and further purification by crystallization (dichloromethane/hexane) as a yellow solid (130 mg, 56%). MS (EI) 460.1 [(M)⁺]; mp 268°C.

Example 79

5-{5-[5-(3-Fluoro-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyrimidin-2-ylamine

The title compound was prepared from 5-(3-fluoro-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.18) (197 mg, 0.5 mmol) and 2-amino-N-hydroxy-pyrimidine-5-carboxamide (example B.5) (115 mg, 0.75 mmol) according to general procedure II. Obtained after flash chromatography on silica gel (ethyl acetate/heptane) and further purification by crystallization (dichloromethane/hexane) as a yellow solid (130 mg, 51%). MS (EI) 510.1 [(M)⁺]; mp 270°C.

Example 80

5-{5-[5-(3-Chloro-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyrimidin-2-ylamine

The title compound was prepared from 5-(3-chloro-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.17) (205 mg, 0.5 mmol) and 2-amino-N-hydroxy-pyrimidine-5-carboxamide (example B.5) (115 mg, 0.75 mmol) according to general procedure II. Obtained after flash chromatography on silica gel (ethyl acetate/heptane) and further purification by crystallization (dichloromethane/hexane) as a yellow solid (150 mg, 57%). MS (EI) 526.1 [(M)⁺]; mp 279°C.

Example 81

5-{5-[5-(3,4-Dichloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyrimidin-2-ylamine

The title compound was prepared from 5-(3,4-dichloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.9) (188 mg, 0.5 mmol) and 2-amino-N-hydroxy-pyrimidine-5-carboxamide (example B.5) (115 mg, 0.75 mmol) according to general procedure II. Obtained after flash chromatography on silica gel (ethyl acetate/heptane) and further purification by crystallization (dichloromethane/hexane) as a yellow solid (180 mg, 73%). MS (EI) 492.0 [(M)⁺]; mp 300°C.

Example 82

5-{5-[5-(4-Chloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyrimidin-2-ylamine

The title compound was prepared from 5-(4-chloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.4) (171 mg, 0.5 mmol) and 2-amino-N-hydroxy-pyrimidine-5-carboxamide (example B.5) (115 mg, 0.75 mmol) according to general procedure II. Obtained after flash chromatography on silica gel (ethyl acetate/heptane) and further purification by crystallization (dichloromethane/hexane) as a yellow solid (165 mg, 72%). MS (EI) 458.1 [(M)⁺]; mp 268°C.

Example 83

5-{5-[5-(3-Methyl-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyrimidin-2-ylamine

The title compound was prepared from 5-(3-methyl-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.8) (195 mg, 0.5 mmol) and 2-amino-N-hydroxy-pyrimidine-5-carboxamide (example B.5) (115 mg, 0.75 mmol) according to general procedure II. Obtained after purification by flash chromatography (ethyl acetate/heptane) and crystallization (dichloromethane/hexane) as a yellow solid (143 mg, 56%). MS (EI) 506.1 [(M)⁺]; mp 272°C.

Example 84

5-{5-[5-(4-Chloro-3-methyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyrimidin-2-ylamine

10 The title compound was prepared from 5-(4-chloro-3-methyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.6) (178 mg, 0.5 mmol) and 2-amino-N-hydroxy-pyrimidine-5-carboxamide (example B.5) (115 mg, 0.75 mmol) according to general procedure II. Obtained after flash chromatography on silica gel (ethyl acetate/heptane) and further purification by crystallization (dichloromethane/hexane) as a yellow solid (54 mg, 23%). MS (EI) 472.1 [(M)⁺]; mp 272°C.

Example 85

4-{5-[5-(4-Chloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine

20 The title compound was prepared from 5-(4-chloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.4) (171 mg, 0.5 mmol) and 2-amino-N-hydroxy-pyridine-4-carboxamide (example B.6) (114 mg, 0.75 mmol) according to general procedure II. Obtained after trituration with water and further purification by crystallization (dichloromethane/ hexane) as a yellow solid (112 mg, 49%). MS (EI) 457.1 [(M)⁺]; mp 252°C.

Example 86

4-{5-[5-(3,4-Dichloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine

The title compound was prepared from 5-(3,4-chloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.9) (188 mg, 0.5 mmol) and 2-amino-N-hydroxy-pyridine-4-carboxamide (example B.6) (114 mg, 0.75 mmol) according to general procedure II. Obtained after trituration with water and further purification by crystallization (dichloromethane/ hexane) as a yellow solid (149 mg, 61%). MS (EI) 491.0 [(M)⁺]; mp 262°C.

Example 87

4-{5-[5-(3-Methyl-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridine-2-ylamine

The title compound was prepared from 5-(3-methyl-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (example C.8) (195 mg, 0.5 mmol) and 2-amino-N-hydroxy-pyridine-4-carboxamide (example B.6) (114 mg, 0.75 mmol) according to general procedure II. Obtained after trituration with water and further purification by crystallization (dichloromethane/hexane) as a yellow solid (167 mg, 66%). MS (EI) 505.2 [(M)⁺]; mp 245°C.

Preparation of pharmaceutical compositions comprising compounds of the invention:

Example I

Tablets of the following composition are produced in a conventional manner:

	<u>mg/Tablet</u>
Active ingredient	100
Powdered. lactose	95
White corn starch	35
Polyvinylpyrrolidone	8
Na carboxymethylstarch	10
Magnesium stearate	2
Tablet weight	<u>250</u>

- 74 -

Example II

Tablets of the following composition are produced in a conventional manner:

	<u>mg/Tablet</u>
Active ingredient	200
5 Powdered. lactose	100
White corn starch	64
Polyvinylpyrrolidone	12
Na carboxymethylstarch	20
Magnesium stearate	4
10 Tablet weight	<u>400</u>

Example III

Capsules of the following composition are produced:

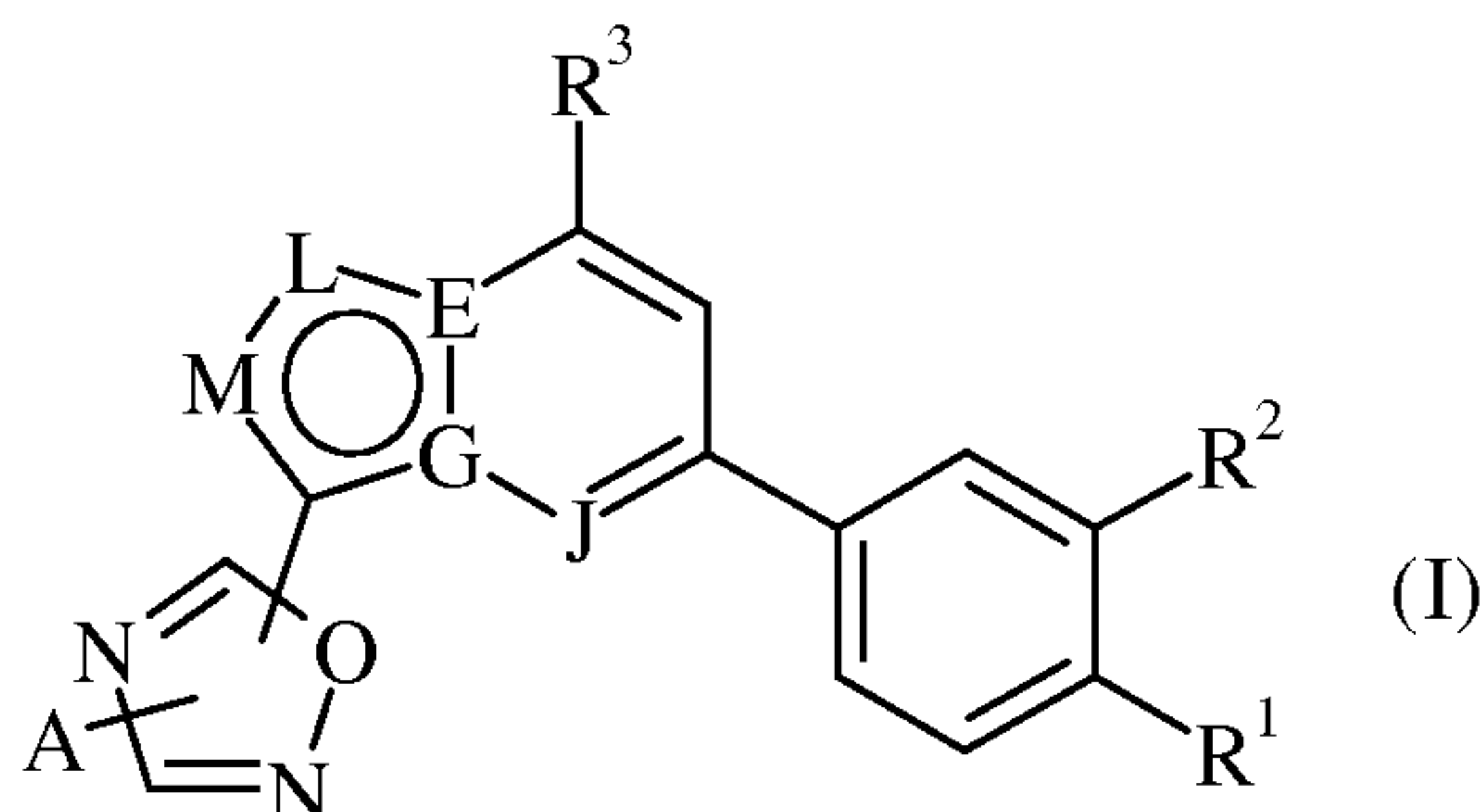
	<u>mg/Capsule</u>
15 Active ingredient	50
Crystalline. lactose	60
Microcrystalline cellulose	34
Talc	5
Magnesium stearate	1
20 Capsule fill weight	<u>150</u>

The active ingredient having a suitable particle size, the crystalline lactose and the microcrystalline cellulose are homogeneously mixed with one another, sieved and thereafter talc and magnesium stearate are admixed. The final mixture is filled into hard
25 gelatine capsules of suitable size.

- 75 -

Claims

1. A compound of general formula (I):



wherein

- 5 either E and J are N, G is C and one of L or M is N and the other is CH;
or L and G are N, E is C, and J and M are CH;

R^1 and R^2 are independently from each other H, halogen, C_{1-6} -alkyl optionally substituted by one or more F or by C_{1-6} -alkoxy, C_{1-6} -alkoxy optionally substituted by one or more F;

- 10 R^3 is H, $-C(CH_3)_2OH$, linear C_{1-4} -alkyl or C_{3-4} -cycloalkyl which are optionally substituted by one or more substituent(s) selected from the group consisting of 1 to 6 F and 1 to 2 OH;

A is selected from the group consisting of aryl or 5 or 6-membered heteroaryl optionally substituted by one to four R^a ;

- 15 R^a is F, OH, amino, C_{1-6} -alkyl optionally substituted by OH, C_{1-6} -alkoxy, C_{3-4} -cycloalkyl, $-CO-R^b$, SO_2-R^c or $SO_2-NR^dR^e$;

R^b is amino;

R^c is OH or C_{1-6} -alkyl;

- R^d and R^e can be the same or can be different from each others and are selected from the
20 group consisting of:

H;

straight or branched C_{1-6} -alkyl optionally substituted by one or more substituent(s) selected from the group consisting of F, cyano, OH, di(C_{1-6} -alkyl)amino, C_{3-6} -cycloalkyl, 5 or 6-membered heterocycloalkyl, aryl or 5 or 6-membered heteroaryl;

25

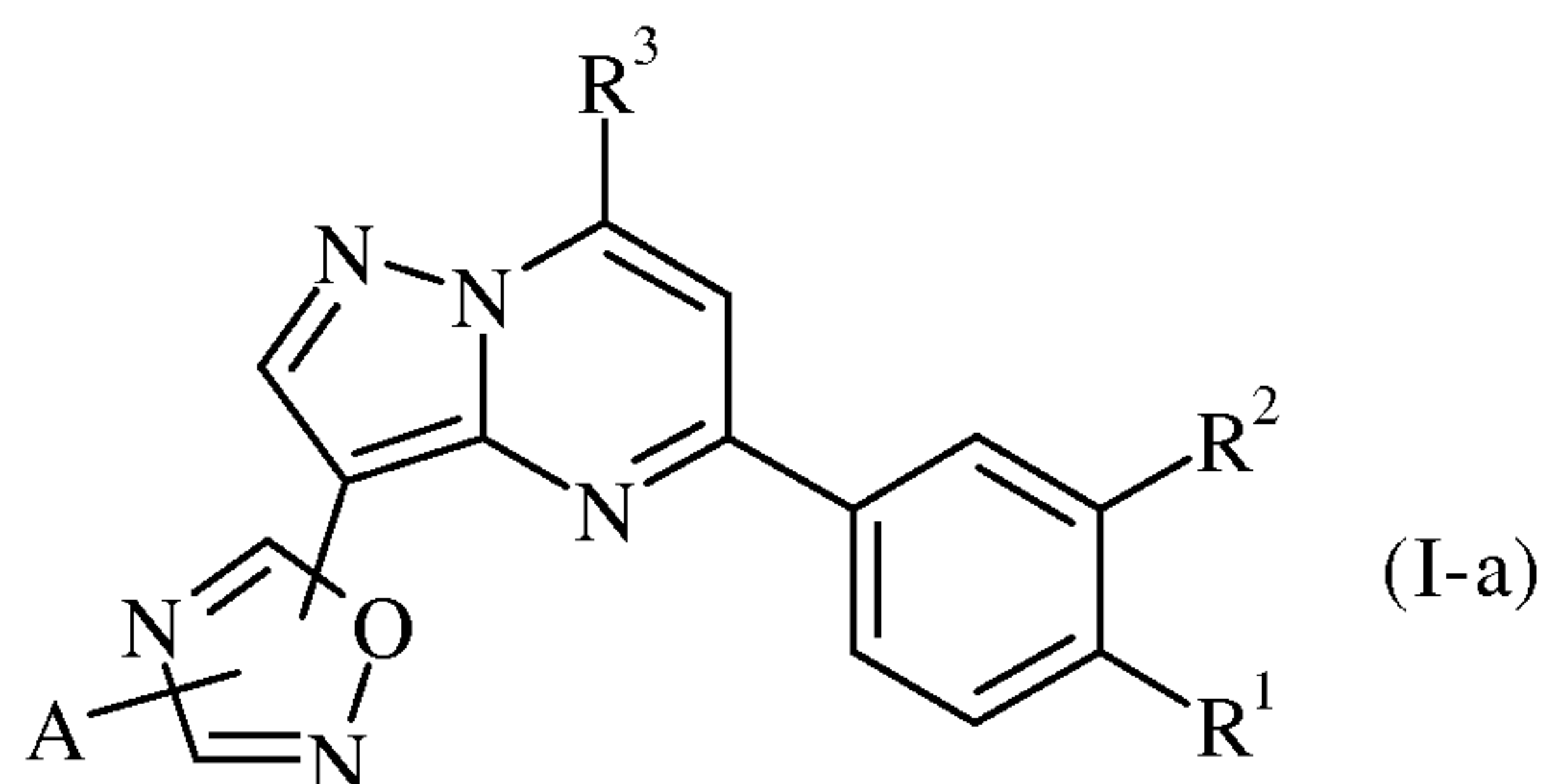
C_{3-6} -cycloalkyl;

aryl; or

5 or 6-membered heteroaryl;

or R^d and R^e may, together with the nitrogen atom to which they are attached, form an heterocyclic ring of 4 to 6 ring members which may be substituted by OH or C_{1-6} -alkyl; as well as pharmaceutically acceptable salts thereof.

2. A compound of formula (I-a) according to claim 1:



wherein A and R^1 to R^3 are as defined in claim 1.

3. The compound of formula (I-a) according to claim 2, wherein:

R^1 is halo or CF_3 ;

R^2 is H, halo, C_{1-6} -alkyl or C_{1-6} -alkoxy optionally substituted by one or more F;

R^3 is H, linear C_{1-4} -alkyl, preferably methyl or C_{3-4} -cycloalkyl which are optionally substituted by 1 to 6 F;

A is selected from the group consisting of aryl or 5 or 6-membered heteroaryl which are optionally substituted by one to four R^a ;

R^a is amino or $SO_2-NR^dR^e$; with R^d and R^e are H;

as well as pharmaceutically acceptable salts thereof.

4. The compound of formula (I-a) according to claim 3, wherein:

R^1 is Cl, F or CF_3 ;

R^2 is H, F, Cl, methyl, OEt, CHF_2 , CF_3 , OCF_3 or OCH_2CF_3 ;

R^3 is H, methyl or cyclopropyl, which are optionally substituted by 2 or 3 F;

A is selected from the group consisting of phenyl, thiophenyl, pyridinyl, pyrimidinyl or pyrazolyl, optionally substituted by one R^a ;

R^a is amino or $SO_2-NR^dR^e$; with R^d and R^e are H;

as well as pharmaceutically acceptable salts thereof.

5. The compound of formula (I-a) according to claim 4, wherein it is selected from the group consisting of:

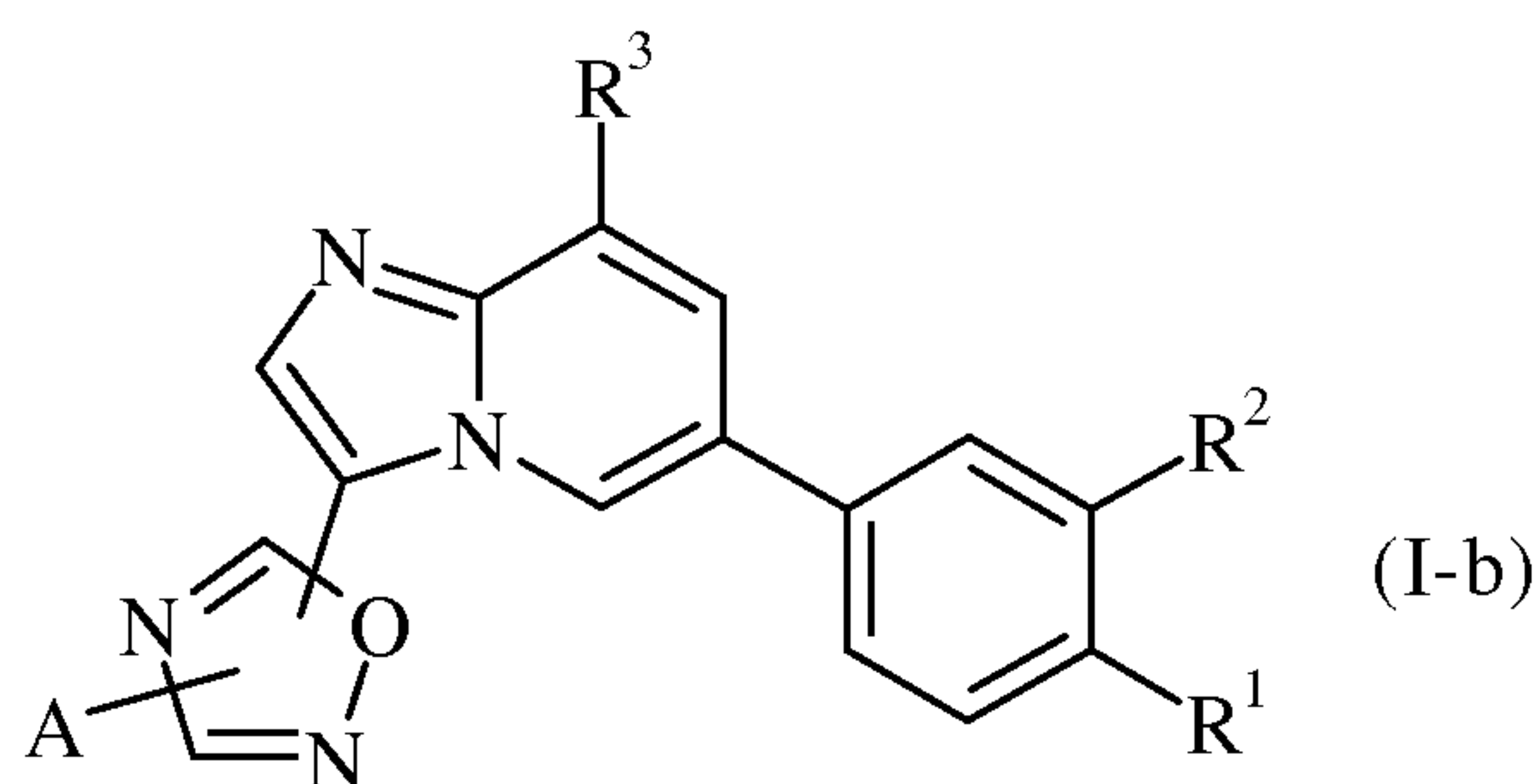
- 4-{5-[7-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 3-{5-[7-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 5 3-(3-Pyridin-3-yl-[1,2,4]oxadiazol-5-yl)-7-trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidine;
- 4-{5-[7-Difluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 3-{5-[7-Difluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 10 3-{5-[5-(4-Chloro-phenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 3-{5-[7-Cyclopropyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 15 4-{5-[5-(4-Chloro-phenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 4-{5-[7-Cyclopropyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 3-{5-[5-(4-Chloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 20 4-{5-[5-(4-Chloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 4-{3-[7-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-5-yl}-benzenesulfonamide;
- 25 3-{3-[7-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-5-yl}-benzenesulfonamide;
- 3-(5-{5-[3-(2,2,2-Trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 3-{5-[5-(3-Methyl-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 30 a)pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 4-{5-[5-(3-Methyl-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 3-{5-[5-(4-Chloro-phenyl)-7-difluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;

- 5- {5-[5-(4-Chloro-phenyl)-7-cyclopropyl-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide;
- 5- {5-[5-(3-Methyl-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-
a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide;
- 5 5-(5-{5-[3-(2,2,2-Trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-7-trifluoromethyl-
pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl)-thiophene-2-sulfonic acid amide;
- 5- {5-[7-Cyclopropyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-
yl]-[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide;
- 4- {5-[7-Trifluoromethyl-5-(3-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-
10 3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 3- {5-[7-Trifluoromethyl-5-(3-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-
3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 5- {5-[7-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-
3-yl]-[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide;
- 15 5- {5-[5-(4-Chloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide;
- 5- {5-[5-(4-Chloro-phenyl)-7-difluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide;
- 5- {5-[7-Methyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-
20 [1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide;
- 5- {5-[7-Difluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-
yl]-[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide;
- 5- {5-[5-(4-Chloro-phenyl)-7-methyl-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide;
- 25 5- {3-[7-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-
3-yl]-[1,2,4]oxadiazol-5-yl}-thiophene-2-sulfonic acid amide;
- 5- {5-[7-Trifluoromethyl-5-(3-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-
3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 5- {5-[7-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-
30 3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 5- {5-[7-Difluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-
yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 5- {5-[5-(3-Methyl-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-
a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;

- 3-{5-[5-(4-Chloro-phenyl)-7-methyl-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 5- {5-[7-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-
3-yl]-[1,2,4]oxadiazol-3-yl}-pyrimidin-2-ylamine;
- 5 3-{5-[5-(4-Chloro-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-
benzenesulfonamide;
- 5- {5-[5-(4-Trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide;
- 3-{5-[5-(4-Trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-
10 [1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 4-{5-[7-Trifluoromethyl-5-(4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-
3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 4-{5-[5-(4-Trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 15 5-{5-[5-(4-Chloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 5-{5-[5-(4-Chloro-phenyl)-7-difluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 5-{5-[5-(4-Chloro-3-methyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-
20 3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 5-{5-[7-Difluoromethyl-5-(3-methyl-4-trifluoromethyl-phenyl)-pyrazolo[1,5-
a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 5-{5-[5-(3,4-Dichloro-phenyl)-7-difluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 25 5-{5-[5-(3,4-Dichloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-
[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 5-{5-[7-Difluoromethyl-5-(3-ethoxy-4-trifluoromethyl-phenyl)-pyrazolo[1,5-
a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 5-{5-[5-(3-Ethoxy-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-
30 a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 5-(5-{5-[3-(2,2,2-Trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-7-trifluoromethyl-
pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl)-pyridin-2-ylamine;
- 5-(5-{7-Difluoromethyl-5-[3-(2,2,2-trifluoro-ethoxy)-4-trifluoromethyl-phenyl]-
pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl)-pyridin-2-ylamine;

- 5- {5-[5-(3-Chloro-4-trifluoromethyl-phenyl)-7-difluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 5- {5-[5-(3-Chloro-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 5 5- {5-[7-Difluoromethyl-5-(3-fluoro-4-trifluoromethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 5- {5-[5-(3-Fluoro-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 5- {5-[5-(3,4-Difluoro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 10 [1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 5- {5-[5-(4-Chloro-3-methyl-phenyl)-7-difluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 5- {5-[5-(3,4-Difluoro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyrimidin-2-ylamine;
- 15 5- {5-[5-(3-Fluoro-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyrimidin-2-ylamine;
- 5- {5-[5-(3-Chloro-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyrimidin-2-ylamine;
- 5- {5-[5-(3,4-Dichloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyrimidin-2-ylamine;
- 20 [1,2,4]oxadiazol-3-yl}-pyrimidin-2-ylamine;
- 5- {5-[5-(4-Chloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyrimidin-2-ylamine;
- 5- {5-[5-(3-Methyl-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyrimidin-2-ylamine;
- 25 5- {5-[5-(4-Chloro-3-methyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyrimidin-2-ylamine;
- 4- {5-[5-(4-Chloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 4- {5-[5-(3,4-Dichloro-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine; and
- 30 [1,2,4]oxadiazol-3-yl}-pyridine-2-ylamine.
- 4- {5-[5-(3-Methyl-4-trifluoromethyl-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-[1,2,4]oxadiazol-3-yl}-pyridine-2-ylamine.

6. A compound of formula (I-b) according to claim 1:



wherein A and R¹ to R³ are as defined in claim 1.

7. The compound of formula (I-b) according to claim 6, wherein:

- R¹ is halo or CF₃;
- 5 R² is H, halo, C₁₋₆-alkyl or C₁₋₆-alkoxy optionally substituted by one or more F;
- R³ is H, linear C₁₋₄-alkyl, preferably methyl or C₃₋₄-cycloalkyl which are optionally substituted by 1 to 6 F;
- A is selected from the group consisting of aryl or 5 or 6-membered heteroaryl which are optionally substituted by one to four R^a;
- 10 R^a is amino or SO₂-NR^dR^e; with R^d and R^e are H;
- as well as pharmaceutically acceptable salts thereof.

8. The compound of formula (I-b) according to claim 7, wherein:

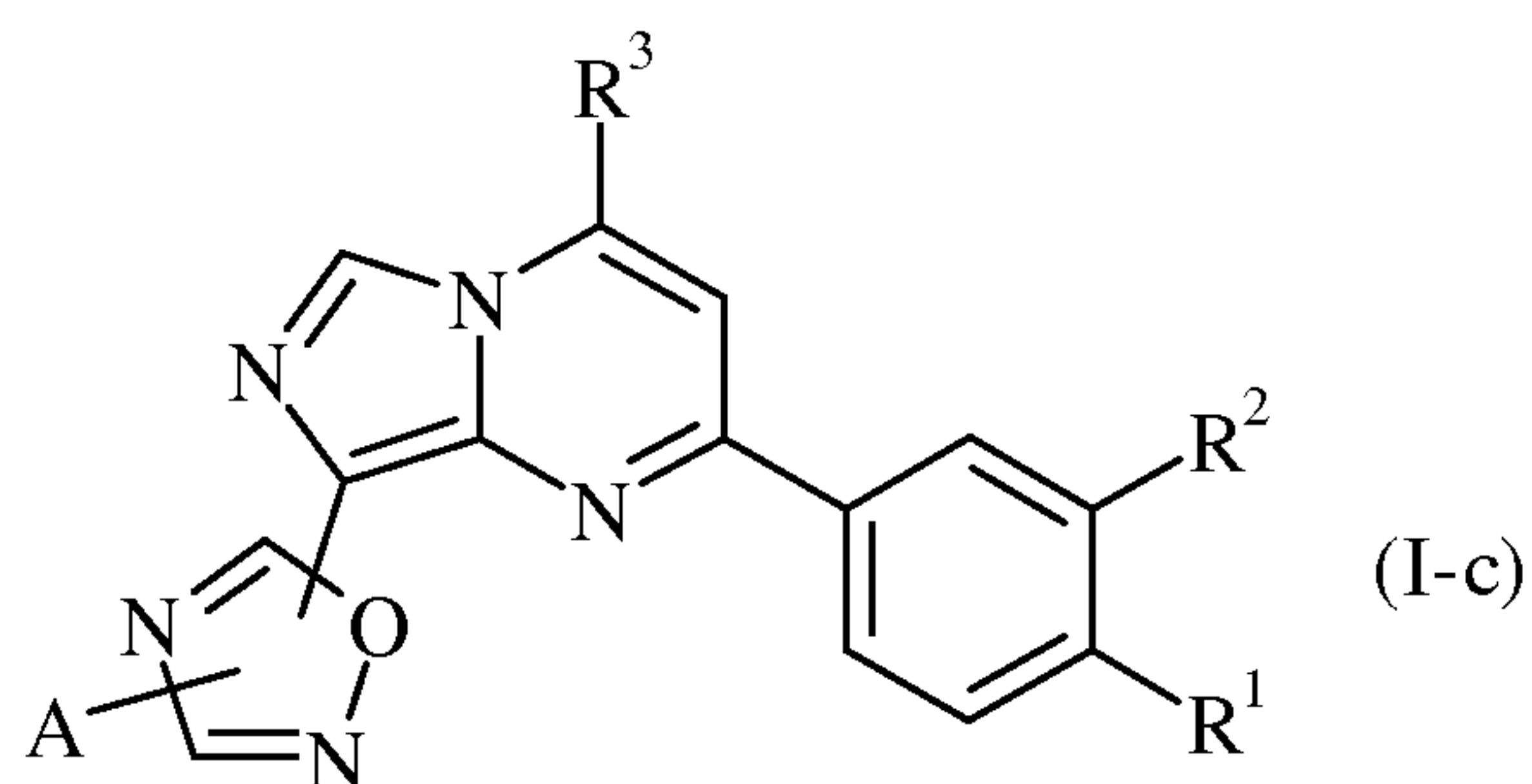
- R¹ is Cl, F or CF₃;
- R² is H, F, Cl, methyl, OEt, CHF₂, CF₃, OCF₃ or OCH₂CF₃;
- 15 R³ is H, methyl or cyclopropyl, which are optionally substituted by 2 or 3 F;
- A is selected from the group consisting of phenyl, thiophenyl, pyridinyl, pyrimidinyl or pyrazolyl, optionally substituted by one R^a;
- R^a is amino or SO₂-NR^dR^e; with R^d and R^e are H;
- as well as pharmaceutically acceptable salts thereof.

20 9. The compound of formula (I-b) according to claim 8, wherein it is selected from the group consisting of:

- 3-{5-[8-Trifluoromethyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 4-{5-[8-Trifluoromethyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 25 4-{5-[6-(4-Chloro-phenyl)-8-methyl-imidazo[1,2-a]pyridin-3-yl]-[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;

- 3-{5-[6-(4-Chloro-phenyl)-8-methyl-imidazo[1,2-a]pyridin-3-yl]-
[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 5- {5-[6-(4-Chloro-phenyl)-8-methyl-imidazo[1,2-a]pyridin-3-yl]-
[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide;
- 5 4-{5-[8-Methyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-
[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 3-{5-[8-Methyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-
[1,2,4]oxadiazol-3-yl}-benzenesulfonamide;
- 5- {5-[8-Methyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-
10 [1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide;
- 5- {5-[8-Methyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-
[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine;
- 5- {5-[8-Methyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-
[1,2,4]oxadiazol-3-yl}-pyrimidin-2-ylamine;
- 15 4-{5-[6-(4-Trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-[1,2,4]oxadiazol-
3-yl}-benzenesulfonamide;
- 3-{5-[6-(4-Trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-[1,2,4]oxadiazol-
3-yl}-benzenesulfonamide;
- 5- {5-[6-(4-Trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-[1,2,4]oxadiazol-
20 3-yl}-thiophene-2-sulfonic acid amide;
- 5- {5-[6-(4-Chloro-phenyl)-imidazo[1,2-a]pyridin-3-yl]-[1,2,4]oxadiazol-3-yl}-
thiophene-2-sulfonic acid amide;
- 5- {5-[6-(4-Trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-[1,2,4]oxadiazol-
3-yl}-pyridin-2-ylamine;
- 25 5- {5-[6-(4-Chloro-phenyl)-imidazo[1,2-a]pyridin-3-yl]-[1,2,4]oxadiazol-3-yl}-
pyridin-2-ylamine;
- 4-{5-[8-Methyl-6-(4-trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-
[1,2,4]oxadiazol-3-yl}-pyridin-2-ylamine; and
- 4-{5-[6-(4-Trifluoromethyl-phenyl)-imidazo[1,2-a]pyridin-3-yl]-[1,2,4]oxadiazol-
30 3-yl}-pyridin-2-ylamine.

10. A compound of formula (I-c) according to claim 1:



wherein A and R¹ to R³ are as defined in claim 1.

11. The compound of formula (I-c) according to claim 10, wherein:

- R¹ is halo or CF₃;
- 5 R² is H, halo, C₁₋₆-alkyl or C₁₋₆-alkoxy optionally substituted by one or more F;
- R³ is H, linear C₁₋₄-alkyl, preferably methyl or C₃₋₄-cycloalkyl which are optionally substituted by 1 to 6 F;
- A is selected from the group consisting of aryl or 5 or 6-membered heteroaryl which are optionally substituted by one to four R^a;
- 10 R^a is amino or SO₂-NR^dR^e; with R^d and R^e are H;
- as well as pharmaceutically acceptable salts thereof.

12. The compound of formula (I-c) according to claim 11, wherein:

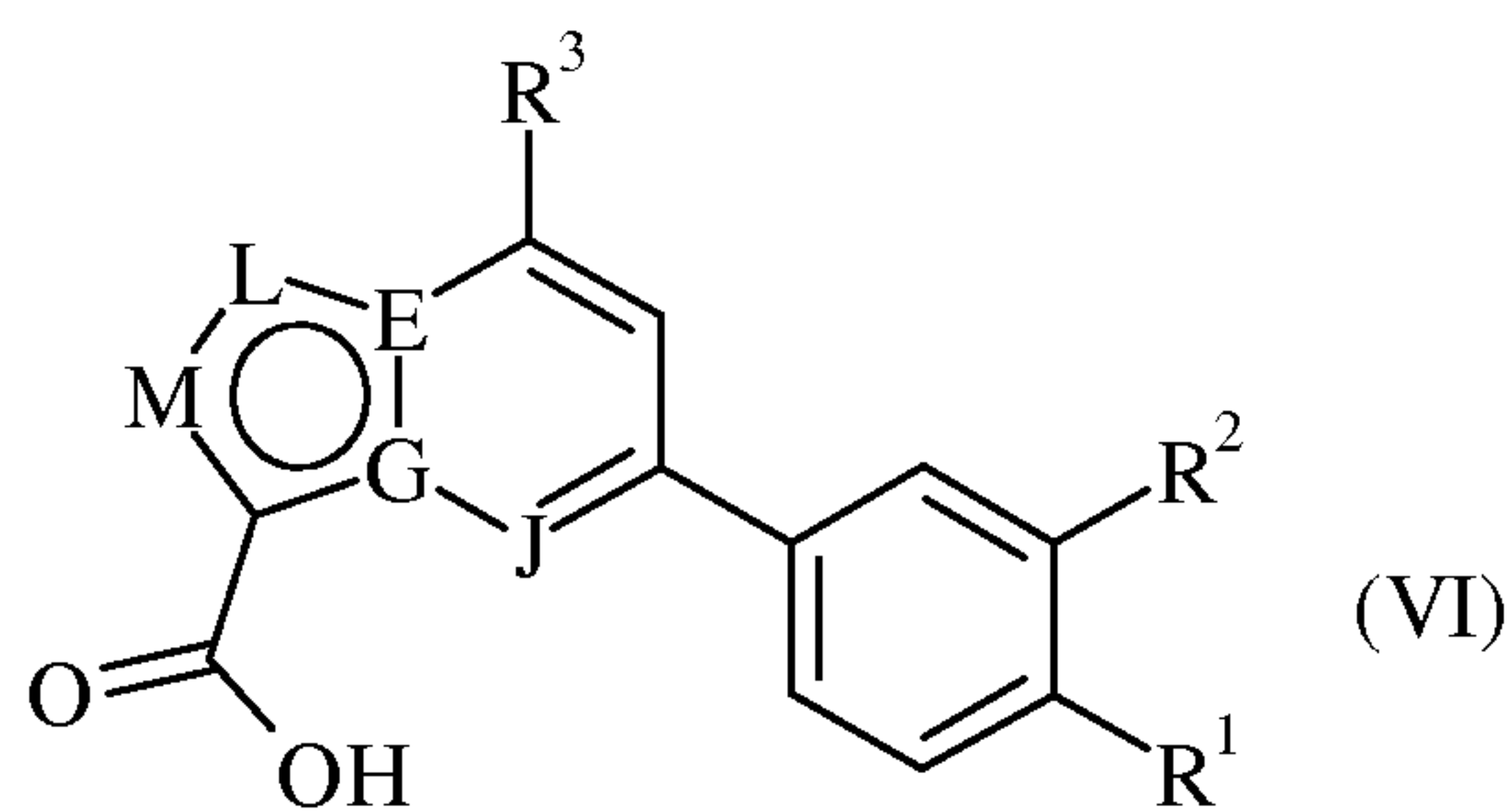
- R¹ is Cl, F or CF₃;
- R² is H, F, Cl, methyl, OEt, CHF₂, CF₃, OCF₃ or OCH₂CF₃;
- 15 R³ is H, methyl or cyclopropyl, which are optionally substituted by 2 or 3 F;
- A is selected from the group consisting of phenyl, thiophenyl, pyridinyl, pyrimidinyl or pyrazolyl, optionally substituted by one R^a;
- R^a is amino or SO₂-NR^dR^e; with R^d and R^e are H;
- as well as pharmaceutically acceptable salts thereof.

20 13. The compound of formula (I-c) according to claim 12, wherein it is selected from the group consisting of:

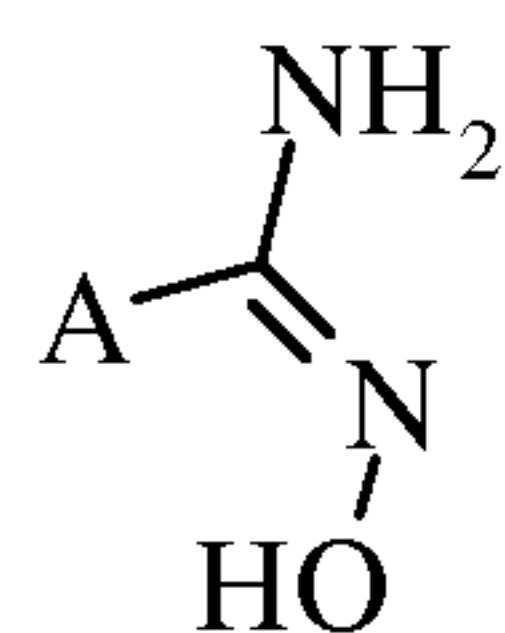
- 4-{3-[4-Trifluoromethyl-2-(4-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidin-8-yl]-[1,2,4]oxadiazol-5-yl}-benzenesulfonamide; and
- 5-{5-[4-Trifluoromethyl-2-(4-trifluoromethyl-phenyl)-imidazo[1,5-a]pyrimidin-8-yl]-[1,2,4]oxadiazol-3-yl}-thiophene-2-sulfonic acid amide.
- 25

14. A process for the preparation of the compounds of formula (I) according to any one of claims 1 to 13, comprising the steps of:

a) either reacting a compound of formula (VI):

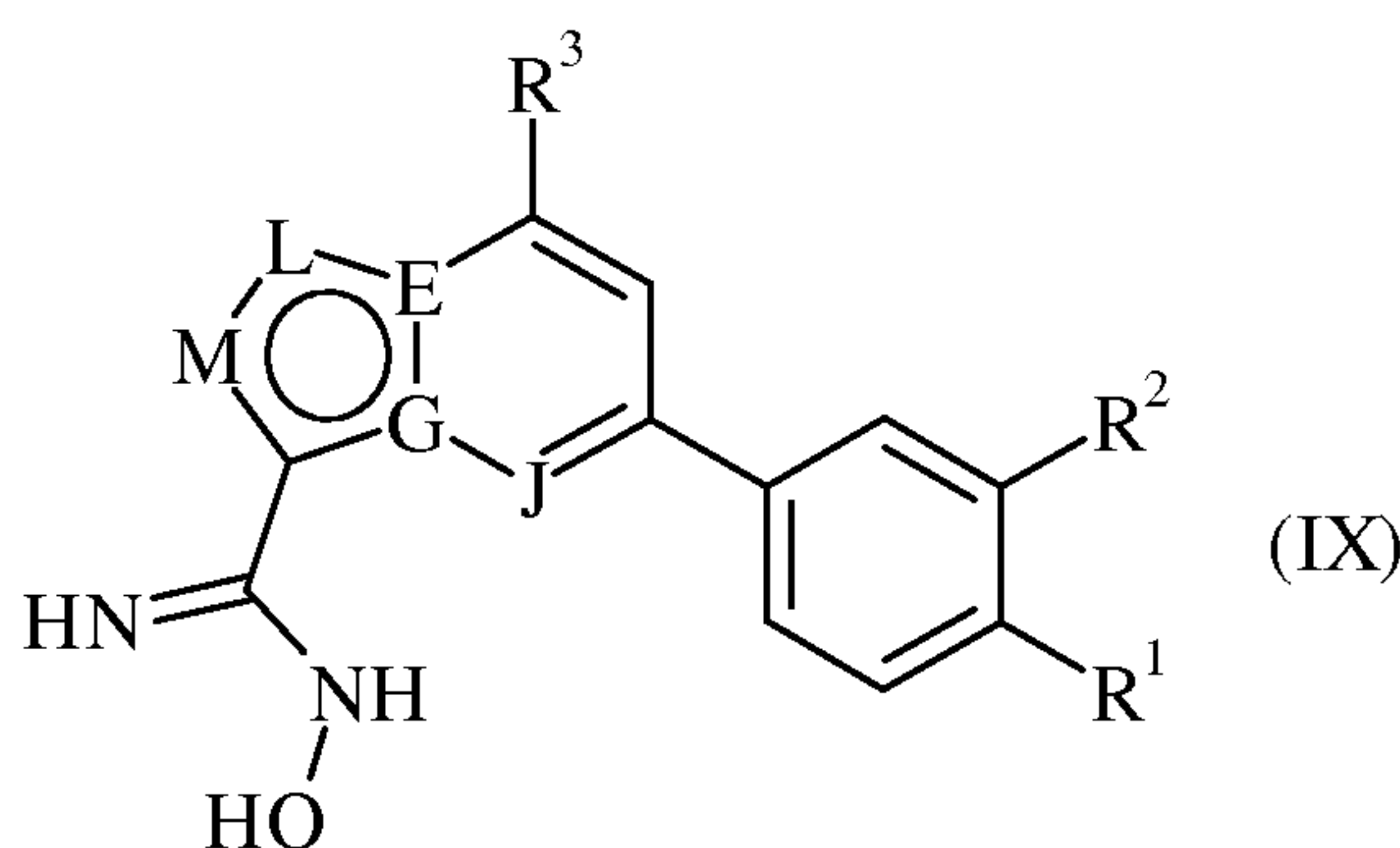


with a compound of formula (VIII):

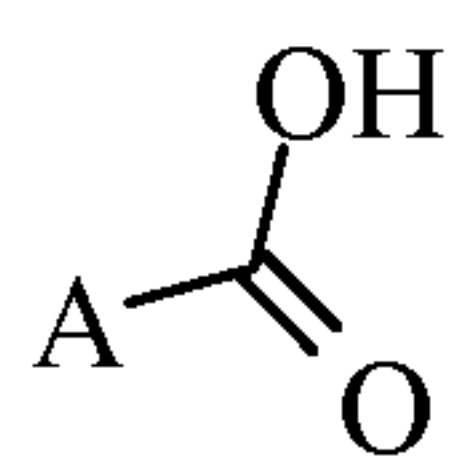


(VIII)

5 b) or reacting a compound of formula (IX):



with a compound of formulae (X)



(X)

10 to obtain a compound of formula I, wherein R¹ to R³ and A are as defined hereinabove in connection with formula (I).

15. A compound prepared according to claim 14.

16. A pharmaceutical composition containing a compound according to any one of claims 1 to 13 for the prevention or the treatment of a disease or condition in which
15 mGluR2 activation plays a role or is implicated.

17. The pharmaceutical composition according to claim 16 wherein the prevention or the treatment of acute and/or chronic neurological disorders such as psychosis, schizophrenia, Alzheimer's disease, cognitive disorders, memory deficits, colon cancer, sleep disorders, disorders of circadian rhythms and glioma.

5 18. Use of a compound according to any one of claims 1 to 13 for the manufacture of a medicament for the treatment or prevention of a disease or condition in which mGluR2 activation plays a role or is implicated.

10 19. The use according to claim 18 for the treatment and/or prevention of acute and/or chronic neurological disorders comprising psychosis, schizophrenia, Alzheimer's disease, cognitive disorders, memory deficits, colon cancer, sleep disorders, disorders of circadian rhythms and glioma.

20. The invention as hereinbefore described.

