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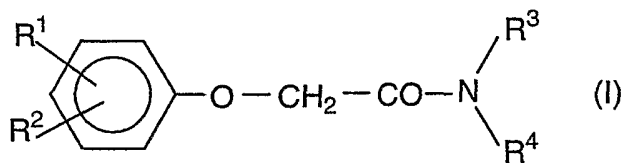
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[Continued on next page]

(54) Title: NEW ARYLOXY ACETIC ACID AMIDE DERIVATIVES



(I)

carbon atoms of the benzyl group, R^3 and R^4 mean the same or different C_{1-4} alkyl groups which are substituted by phenyl group, or R^3 and R^4 mean together a C_{4-6} alkylene chain which can be interrupted optionally by a nitrogen atom and which can contain a C-C double bond and which C_{4-6} alkylene chain can substituted by one or two substituents from the following hydroxy group, phenyl or phenoxy group optionally substituted by a C_{1-4} alkyl or trifluoro methyl group, =CH-phenyl group which can be substituted by halogen atom or C_{1-4} alkyl group, C_{1-4} alkyl group optionally substituted by hydroxy group and one or two phenyl groups which can be substituted by halogen atom or C_{1-4} alkyl group, C_{1-4} alkyl amino group which is substituted by a phenyl or naphthyl group which can be substituted optionally by a halogen atom or a C_{1-4} alkyl group, as well as their salts formed with organic or inorganic acids or bases and solvates of these compounds are functional antagonists of NMDA receptors, which target the NMDA receptors primarily via binding to the ifenprodil binding site. Furthermore objects of the present invention are the pharmaceutical compositions containing new aryloxy acetic acid amide derivatives of formula (I) or optical antipodes or racemates or the salts thereof as active ingredients and processes for producing these compounds and pharmaceutical compositions.

(57) Abstract: The new aryloxy acetic acid amide derivatives of formula (I) where R^1 and R^2 are the same or different and can be hydrogen atom or C_{1-4} alkanoylamido group optionally substituted by halogen atom or C_{1-4} alkyl-sulfonylamido group or N' -(C_{1-4} alkyl)-ureido group C_{1-6} alkoxy-carbonyl-amido or di-(C_{1-4} alkyl)-amino group with the proviso that only one of them can be hydrogen atom, or R^1 and R^2 form together a -NH-CO-NH-, -NH-N=CH- or -NH-CO-O- chain attached to two neighbouring



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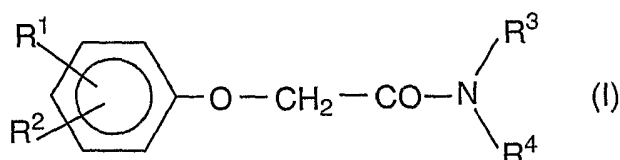
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New aryloxy acetic acid amide derivatives

The invention relates to new aryloxy acetic acid amide derivatives of formula (I)



5 where

R^1 and R^2 are the same or different and can be hydrogen atom or
 C_{1-4} alkanoylamido group optionally by halogen atom substituted or
 C_{1-4} alkyl-sulfonylamido group or
 $\text{N}'\text{-(C}_{1-4}\text{ alkyl)-ureido}$ group

10 C_{1-6} alkoxy-carbonyl-amido or
 $\text{di-(C}_{1-4}\text{ alkyl)-amino}$ group

with the proviso that only one of them can be hydrogen atom, or

R^1 and R^2 form together a -NH-CO-NH- , -NH-N=CH- or -NH-CO-O- chain attached to two
neighbouring carbon atoms of the benzyl group,

15 R^3 and R^4 mean the same or different C_{1-4} alkyl groups which are substituted by phenyl group,
or

R^3 and R^4 mean together a C_{4-6} alkylene chain which can be interrupted optionally by a nitrogen
atom and which can contain a C-C double bond and which C_{4-6} alkylene chain can
substituted by one or two substituents from the following

20 hydroxy group,

phenyl or phenoxy group optionally substituted by a C_{1-4} alkyl or trifluoro methyl
group,

=CH- group, substituted by phenyl group which can be substituted by halogen atom
or C_{1-4} alkyl group,

25 C_{1-4} alkyl group optionally substituted by hydroxy group and one or two phenyl
groups which can be substituted by halogen atom or C_{1-4} alkyl group,

C_{1-4} alkyl amino group which is substituted by a phenyl or naphthyl group which can
be substituted optionally by a halogen atom or a C_{1-4} alkyl group,

as well as their salts formed with organic or inorganic acids or bases and solvates of these compounds

which are antagonists of NMDA receptor or are intermediates for preparing thereof.

Background of the invention.

5 N-methyl-D-aspartate (NMDA) receptors are ligand-gated cation-channels embedded in the cell membranes of neurons. Overactivation of NMDA receptors by glutamate, their natural ligand, can lead to calcium overload of cells. This triggers a cascade of intracellular events that alters the cell function and ultimately may lead to death of neurons [TINS, **10**, 299-302 (1987)]. Antagonists of the NMDA receptors may be used for treating many disorders that
10 are accompanied with excess release of glutamate, the main excitatory neurotransmitter in the central nervous system.

The knowledge on the NMDA receptor structure, function and pharmacology has expanded owing to recent achievements of the molecular biology. The NMDA receptors are heteromeric assemblies built up from at least one NR1 subunit and at least one of the four
15 different NR2 subunits (NR2A-D). Both spatial distributions in the CNS and the pharmacological sensitivity of NMDA receptors built up from various NR2 subunits are different. Particularly interesting of these is the NR2B subunit due to its restricted distribution (highest densities in the forebrain and substantia gelatinosa of the spinal cord). Compounds selective for this subtype are available [Curr. Pharm. Des., **5**, 381-404 (1999)] and have been
20 proved to be effective in animal models of stroke [Stroke, **28**, 2244-2251 (1997)], traumatic brain injury [Brain Res., **792**, 291-298 (1998)], Parkinson's disease [Exp. Neurol., **163**, 239-243 (2000)], neuropathic and inflammatory pain [Neuropharmacology, **38**, 611-623 (1999)]. Moreover, NR2B subtype selective antagonists of NMDA receptors are expected to possess little or no untoward side effects that are typically caused by the non-selective antagonists of NMDA
25 receptors, namely psychotomimetic effects such as dizziness, headache, hallucinations, dysphoria and disturbances of cognitive and motor function.

NR2B subtype selective NMDA antagonism can be achieved with compounds that specifically bind to, and act on, an allosteric modulatory site of the NR2B subunit containing receptors. This binding site can be characterised by displacement (binding) studies with specific
30 radioligands, such as [125I]-ifenprodil [J.Neurochem., **61**, 120-126 (1993)] or [3H]-Ro 25,6981 [J. Neurochem., **70**, 2147-2155 (1998)]. Since ifenprodil was the first, though not sufficiently specific, known ligand of this receptor, it has also been termed ifenprodil binding site.

The patent document WO01/30330 discloses a method to treat pain utilizing 2-methyl- or -ethyl-piperidino-benzimidazole derivatives as NMDA NR2B antagonists.

Aralkyl- and aralkenyl-piperidino-derivates are described as NMDA receptor antagonists in the published patent application WO99/48891.

5 The published PCT application WO 99/21539 discloses a method for treating disease-related or drug-induced dyskinesias using NMDA receptor antagonists. The used compounds consist of a substituted piperidine ring and a substituted aryl or heteroaryl group, which are coupled by a (hetero) alkylene chain or a direct chemical bound.

6-{3-[4-(4-Fluorobenzyl)-piperidin-1-yl]-propionyl}-3H-benzoxazol-2-one

10 derivatives are published as excitatory amino acid antagonists in the PCT application WO98/18793.

A large number of 4-substituted piperidine analogs and their use as subtype selective NMDA receptor antagonists are disclosed in the PCT application WO 97/23216. Another group of compounds of this type act on the glutamate receptor and on the glutamate receptor dependent ion channel as disclosed in the published German patent application DE 4410822.

Summary of the invention

Surprisingly it was found that the new aryloxy acetic acid amide derivatives of formula (I) of the present invention are functional antagonists of NMDA receptors, which target the NMDA receptors primarily via binding to the ifenprodil binding site. Therefore, they are believed to be NR2B subtype specific antagonists.

Experimental protocols

Expression of recombinant NMDA receptors

To prove NR2B selectivity of our compounds, we tested them on cell lines stably expressing recombinant NMDA receptors with subunit compositions of NR1(-3)/NR2A. cDNAs of human NR1(-3) and NR2A subunits subcloned into inducible mammalian expression vectors were introduced into HEK 293 cells lacking NMDA receptors using a cationic lipid-mediated transfection method [Biotechniques, 1997 May ;22(5): 982-7; Neurochemistry International, 43, 19-29. (2003)]. Resistance to neomycin and hygromycin was used to screen for clones possessing both vectors and monoclonal cell lines were established from the clones producing the highest response to NMDA exposure. Compounds were tested for their inhibitory action on NMDA evoked cytosolic calcium elevations in fluorescent calcium measurements. Studies were performed 48-72 h after addition of the inducing agent. Ketamine (500 µM) was also present during the induction in order to prevent cytotoxicity.

Assessment of NMDA antagonist potency *in vitro* by measurement of intracellular calcium concentration with a plate reader fluorimeter in cells expressing recombinant NMDA receptors

Measurements of $[Ca^{2+}]_i$ were carried out on EcR HEK293 cells stably expressing the murine NR1a/NR2B NMDA receptor subunit combinations. Cells were grown in standard 96-well microplates and before the measurement were loaded with a fluorescent Ca^{2+} -sensitive dye, fluo-4/AM (2 μ M) for 60-90min. To facilitate dye retention, the loading medium also contained 2 mM probenecid (an anion-transport inhibitor). To stop dye loading cells were washed twice with extracellular medium (140mM NaCl, 5mM KCl, 2mM $CaCl_2$, 5mM HEPES, 5mM HEPES-Na, 20mM glucose, 10 μ M glycine, pH=7.4), containing 2mM probenecid and 400 μ M DL-AP5 (an NMDA-antagonist to prevent deleterious receptor activation during the washing step). After washing, the test compounds (diluted in extracellular medium from a DMSO stock solution, final DMSO concentration was <0.1%) were added to the cells. Cytosolic calcium measurements were carried out with a plate reader fluorimeter (Fluoroskan Ascent, Labsystems): after recording baseline fluorescence (5min.), elevation of $[Ca^{2+}]_i$ was induced by application of 100 μ M NMDA and the fluorescence was recorded for an additional 5 min. Inhibitory potency of the test compounds was assessed by measuring the reduction in the calcium elevation in the presence of different concentrations of the compounds. All treatments on a single plate were measured in multiple wells. The average value of all wells of a treatment was used for analysis.

Dose-response curves and IC_{50} -values were calculated by using data derived from at least three independent experiments. Inhibitory potency of a compound at a single concentration point was expressed as percent inhibition of the NMDA response. Sigmoidal concentration-inhibition curves were fit to the data and IC_{50} values were determined as the concentration that produces half of the maximal inhibition caused by the compound.

Table A.

IC_{50} values of most active compounds measured by fluorimetric method in cells expressing recombinant NMDA receptors.

No.	NR1/NR2B	
	IC_{50} [nM]	n
3b-7	66	4
2a-33	49	4
2a-41	143	4
3b-12	139	2

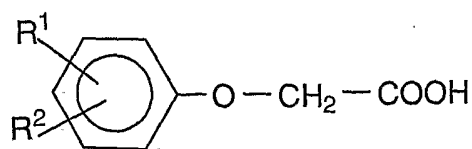
Disorders which may be beneficially treated with NMDA antagonists acting at NR2B site, as reviewed recently by Loftis [Pharmacology & Therapeutics, **97**, 55-85 (2003)] include schizophrenia, Parkinson's disease, Huntington's disease, excitotoxicity evoked by hypoxia and ischemia, seizure disorders, drug abuse, and pain, especially neuropathic, inflammatory and visceral pain of any origin [Eur. J. Pharmacol., **429**, 71-78 (2001)].

Due to their reduced side effect liability compared to non-selective NMDA antagonists, NR2B selective antagonists may have utility in diseases where NMDA antagonists may be effective, such as amyotrophic lateral sclerosis [Neurol. Res., **21**, 309-12 (1999)], withdrawal syndromes of e.g. alcohol, opioids or cocaine [Drug and Alcohol Depend., **59**, 1-15 (2000)], muscular spasms [Neurosci. Lett., **73**, 143-148 (1987)], dementia of various origins [Expert Opin. Investig. Drugs, **9**, 1397-406 (2000)], anxiety, depression, migraine, hypoglycemia, degenerative disorders of the retina (e.g. CMV retinitis), glaucoma, asthma, tinnitus, hearing loss [Drug News Perspect **11**, 523-569 (1998) and WO 00/00197 international patent application].

Accordingly, effective amounts of the compounds of the invention may be beneficially used for the treatment of traumatic injury of brain or spinal cord, tolerance and/or dependence to opioid treatment of pain, withdrawal syndromes of drugs of abuse e.g. alcohol, opioids or cocaine, ischemic CNS disorders, chronic neurodegenerative disorders, such as e.g. Alzheimer's disease, Parkinson's disease, Huntington's disease, pain and chronic pain states, such as e.g. neuropathic pain.

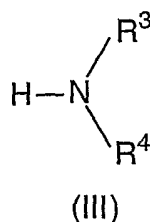
Detailed description of the invention

The new aryloxy acetic acid amide derivatives of formula (I) – wherein the meaning of R¹, R², R³ and R⁴ are as defined in claim 1 – and/or their salts formed with organic or inorganic acids or bases and solvates of these compounds can be prepared by reacting an aryloxy acetic acid of formula (II)



(II)

or a reactive derivative of it - where R¹ and R² have the same meaning as defined in claim 1 - with an secondary amine of formula (III)



- where R^3 and R^4 have the same meaning as defined in claim 1 - and

the obtained compounds of formula (I) - where R^1 , R^2 , R^3 and R^4 are as defined in claim 1 - are transformed in given case into an other compound of formula (I) by introducing further substituents and/or modifying and/or removing the existing ones, and/or formation of salts with acids and/or bases and/or liberating the carboxylic acid amide derivative of formula (I) from the obtained salts by treating with a base and/or acid and/or by forming solvates from them.

A preferably method is when the reactive derivative of the aryloxy acetic acid of formula (II) is formed *in situ* by using of a carbodiimide e.g. by using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) as carbodiimide.

For example the process for producing of compounds of formula (I) can be carried out as follows:

0.25 mmol of an aryloxy acetic acid of formula (II) is solved in 1 ml of dimethylformamide. 0.2 mmol of compound of formula (III) in 1 ml of dimethylformamide, 0.25 mmol of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) in 0.5 ml of dimethylformamide and 0.04 mmol of 4-(dimethylamino)pyridine in 0.5 ml of dichloromethane were added and the mixture was vigorously shaken for 12 hours. The mixture was diluted with 2 ml of dichloromethane, and extracted with 4 ml of 1M HCl three times, 4 ml of water three times, 4 ml of 8 % NaHCO_3 three times and 4 ml of water three times. The organic solution was concentrated to yield the final product (I).

The forming of salts can be performed by known methods, by treating the aryloxy acetic acid amide derivative of formula (I) with acids or bases. From an obtained salt the free aryloxy acetic acid amide derivative of formula (I) can be freed, too by using known methods.

Characterization and Purification Methods

Compounds of the present invention were characterized by high performance liquid chromatography coupled to mass selective detector (LC/MS) using HP 1100 Binary Gradient chromatography system with Microplate Sampler (Agilent, Waldbronn), controlled by ChemStation software. HP diode array detector was used to acquire UV spectra at 225 and 240

nm. All experiments were performed using HP MSD (Agilent, Waldbronn) single quadrupole spectrometer equipped with an electrospray ionisation source to determine the structure.

The synthesized products were dissolved in 1 ml DMSO (Aldrich, Germany). 100 µl of each solution was diluted with DMSO to 1000 µl volume. Analytical chromatographic experiments were performed on Discovery RP C-16 Amide, 5 cm X 4.6 mm X 5 µm column from Supelco (Bellefonte, Pennsylvania) with a flow rate of 1 ml/minute for qualification. The obtained compounds were characterized by their k' value (purity, capacity factor). k' factors are evaluated by the following formula:

$$k' = (t_R - t_0) / t_0$$

where k' = capacity factor, t_R = retention time and t_0 = eluent retention time.

The A eluent was water containing 0.1% trifluoroacetic acid (TFA) (Sigma, Germany), the B eluent was 95% acetonitrile (Merck, Germany) containing 0.1% TFA and 5% A eluent. Gradient elution was used, starting with 100% A eluent and processing to 100% B eluent over a period of 5 minutes.

Semipreparative separation of the compounds of the present invention – purity below 85% - was carried out using the same high performance chromatography system. The separation was performed on Discovery RP C-16 Amide, 20 cm X 10 mm X 5 µm semipreparative column from Supelco (Bellefonte, Pennsylvania) with a flow rate of 3 ml/minutes. The fraction collection was based on mass selective separation. Gradient elution was used, starting with 80% A eluent and processing to 65% B eluent over a period of 35 minutes for those compounds where the capacity factor was more than 2.5. The gradient elution was changed, starting with 100 % A eluent and processing to 55% B eluent in 30 minutes for those compounds where the capacity factor was less than 2.5. The collected fractions were qualified by the above detailed analytical method and the solvent was evaporated by Speed Vac (Savant, USA).

The synthesis of compounds and pharmaceutical compositions according to the invention is illustrated by the following not limiting Examples.

Example 1**5-{2-[4-(4-Chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethoxy}-3H-benzooxazol-2-one (3b-12)**

52 mg (0.25 mmol) (2-Oxo-2,3-dihydro-benzooxazol-5-yl)-oxy-acetic acid is solved in 1 ml of dimethylformamide. 55 mg (0.26 mmol) of 4-(4-chloro-phenoxy)-piperidine in 1 ml of dimethylformamide, 0.25 mmol of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide [EDC] in 0.5 ml of dimethylformamide and 0.04 mmol of 4-(dimethylamino)-pyridine in 0.5 ml of dichloromethane were added and the mixture was vigorously shaken for 12 hours. The mixture was diluted with 2 ml of dichloromethane, and extracted with 4 ml of 1M HCl three times, 4 ml of water three times, 4 ml of 8 % NaHCO₃ three times and 4 ml of water three times. The organic solution was concentrated to yield 49 mg 5-{2-[4-(4-chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethoxy}-3H-benzooxazol-2-one. (k'=3.098)

Using the procedure described above we prepared the following compounds of formula (I). Here and in the following tables Ph means phenyl group. MW_c is the calculated, and MW_m the measured molecular weight.

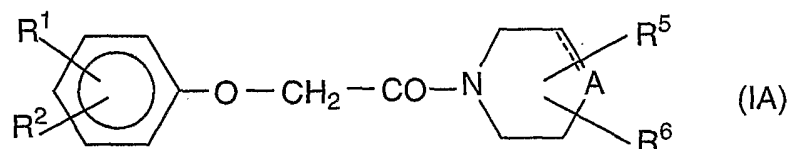
Table 1a

No.	R ¹	R ²	R ³	R ⁴	MW _c	MW _m	k'
1a-1	4- (Et-NH-CO-NH)-	H-	Ph-CH ₂ -CH ₂ -	benzyl-	431.54	432.4	3.188
1a-2	3-acetamido-	H-	Ph-CH ₂ -CH ₂ -	benzyl-	402.50	403.4	3.178
1a-3	4- (tert-butyl-oxy-carbonyl-amino)-	H-	Ph-CH ₂ -CH ₂ -	benzyl-	460.58	461.4	3.637
1a-4	3- (CH ₃) ₂ N-	4-acetamido-	Ph-CH ₂ -CH ₂ -	benzyl-	445.57	446.4	2.529
1a-5	4- CH ₃ -SO ₂ -NH-	H-	Ph-CH ₂ -CH ₂ -	benzyl-	438.55	439.3	3.139
1a-6	4-acetamido-	H-	Ph-CH ₂ -CH ₂ -	benzyl-	402.50	403.4	3.135

Table 1b

No.	R ¹ and R ² together	R ³	R ⁴	MW _c	MW _m	k'
1b-1	3,4- -NH-CO-NH-	Ph-CH ₂ -CH ₂ -	benzyl-	401.47	402.3	3.028
1b-2	3,4- -NH-CO-O-	Ph-CH ₂ -CH ₂ -	benzyl-	402.45	403.3	3.193
1b-3	3,4- -NH-N=CH-	Ph-CH ₂ -CH ₂ -	benzyl-	385.47	386.3	3.232

Using the procedure described above we prepared the following narrower group of compounds of formula (I), covered in the following tables, characterised by the formula (IA), where the dotted bond means a simple C-C bond and A is a -CH₂- group:



5

Table 2a

No.	R ¹	R ²	R ⁵	R ⁶	MW _c	MW _m	k'
2a-1	4- (Et-NH-CO-NH)-	H-	4-benzyl-	H-	395.51	395.51	3.082
2a-2	3-acetamido-	H-	4-benzyl-	H-	366.46	367.2	3.061
2a-3	4- (tert-butyl-oxy-carbonyl-amino)-	H-	4-benzyl-	H-	424.54	425.2	3.544
2a-4	4- CH ₃ -SO ₂ -NH-	H-	4-benzyl-	H-	402.52	403.2	3.018
2a-5	4-acetamido-	H-	4-benzyl-	H-	366.46	367.2	3.013
2a-6	3-acetamido-	H-	4- (Ph-CHOH-)	H-	382.46	383.2	2.396
2a-7	4- (tert-butyl-oxy-carbonyl-amino)-	H-	4- (Ph-CHOH-)	H-	440.54	441.3	2.991
2a-8	4- CH ₃ -SO ₂ -NH-	H-	4- (Ph-CHOH-)	H-	418.52	419.2	2.313
2a-9	4-acetamido-	H-	4- (Ph-CHOH-)	H-	382.46	383.2	2.337
2a-10	4- Et-NH-CO-NH-	H-	4- (4-Cl-Ph-)	4- HO-	431.92	414.1	2.684
2a-11	3-acetamido-	H-	4- (4-Cl-Ph-)	4- HO-	402.88	385.2	2.668
2a-12	4- CH ₃ -SO ₂ -NH-	H-	4- (4-Cl-Ph-)	4- HO-	438.93	421.1	2.606
2a-13	4-acetamido-	H-	4- (4-Cl-Ph-)	4- HO-	402.88	385.1	2.602
2a-14	4- (tert-butyl-oxy-carbonyl-amino)-	H-	4- [4-Cl-Ph-N(CH ₃)-I]	H-	474.00	475.2	2.546
2a-15	4- CH ₃ -SO ₂ -NH-	H-	4- [4-Cl-Ph-N(CH ₃)-I]	H-	451.98	452.3	1.845

2a-16	4- Et-NH-CO-NH-	H-	4- 4-F-benzyl-	H-	413.50	414.2	3.141
2a-17	3-acetamido-	H-	4- 4-F-benzyl-	H-	384.45	385.2	3.129
2a-18	4- CH ₃ -CHCl-CO-NH-	3-acet-amido-	4- 4-F-benzyl-	H-	489.98	490.2	3.054
2a-19	4- (tert-butyl-oxy-carbonyl-amino)-	H-	4- 4-F-benzyl-	H-	442.54	443.2	3.116
2a-20	3-dimethylamino-	4-acetamido-	4- 4-F-benzyl-	H-	427.52	428.2	2.494
2a-21	4- CH ₃ -SO ₂ -NH-	H-	4- 4-F-benzyl-	H-	420.51	421.2	3.088
2a-22	4-acetamido-	H-	4- 4-F-benzyl-	H-	384.45	385.2	3.087
2a-23	4- Et-NH-CO-NH-	H-	4- 4-F-Ph-CH ₂ CH ₂ -	H-	427.52	428.2	3.351
2a-24	3-acetamido-	H-	4- 4-F-Ph-CH ₂ CH ₂ -	H-	398.48	399.2	3.341
2a-25	4- (tert-butyl-oxy-carbonyl-amino)-	H-	4- 4-F-Ph-CH ₂ CH ₂ -	H-	456.56	457.1	3.728
2a-26	3-dimethylamino-	4-acet-amido-	4- 4-F-Ph-CH ₂ CH ₂ -	H-	441.55	442.2	2.765
2a-27	4- (tert-butyl-oxy-carbonyl-amino)-	H-	4- [4-tolyl-N(CH ₃)-]	H-	453.59	454.4	2.489
2a-28	4- CH ₃ -SO ₂ -NH-	H-	4- [4-tolyl-N(CH ₃)-]	H-	431.56	432.5	1.846
2a-29	4- CH ₃ -SO ₂ -NH-	H-	4- 4-F-Ph-NH-	H-	421.49	422.3	1.365
2a-30	4- Et-NH-CO-NH-	H-	4- 4-tolyl-CH ₂ -	H-	409.53	410.4	3.265
2a-31	3-acetamido-	H-	4- 4-tolyl-CH ₂ -	H-	380.49	381.4	3.259

2a-32	3-dimethylamino-	4-acet-amido-	4- 4-tolyl-CH ₂ -	H-	423.56	424.4	2.656
2a-33	4- CH ₃ -SO ₂ -NH-	H-	4- 4-tolyl-CH ₂ -	H-	416.54	417.3	3.217
2a-34	4-acetamido-	H-	4- 4-tolyl-CH ₂ -	H-	380.49	381.3	3.222
2a-35	3-acetamido-	H-	4- [4-Br-Ph-N(CH ₃)-]	H-	460.37	461.3	2.084
2a-36	4-acetamido-	H-	4- [4-Br-Ph-N(CH ₃)-]	H-	460.37	461.2	1.985
2a-37	4- Et-NH-CO-NH-	H-	4- 4-Cl-benzyl-	H-	429.95	430.4	3.327
2a-38	3-acetamido-	H-	4- 4-Cl-benzyl-	H-	400.91	401.3	3.320
2a-39	4- (tert-butyl-oxy-carbonyl-amino)-	H-	4- 4-Cl-benzyl-	H-	458.99	459.3	3.713
2a-40	3-dimethylamino-	4-acet-amido-	4- 4-Cl-benzyl-	H-	443.98	444.4	2.732
2a-41	4- CH ₃ -SO ₂ -NH-	H-	4- 4-Cl-benzyl-	H-	436.96	437.3	3.284
2a-42	4-acetamido-	H-	4- 4-Cl-benzyl-	H-	400.91	401.3	3.284
2a-43	4- Et-NH-CO-NH-	H-	4- 4-Cl-Ph-O-	H-	431.92	432.3	3.117
2a-44	3-acetamido-	H-	4- 4-Cl-Ph-O-	H-	402.88	403.3	3.105
2a-45	4- (tert-butyl-oxy-carbonyl-amino)-	H-	4- 4-Cl-Ph-O-	H-	460.96	461.3	3.548
2a-46	4- CH ₃ -SO ₂ -NH-	H-	4- 4-Cl-Ph-O-	H-	438.93	439.3	3.055
2a-47	4-acetamido-	H-	4- 4-Cl-Ph-O-	H-	402.88	403.3	3.063
2a-48	4- Et-NH-CO-NH-	H-	4- 4-tolyl-O-	H-	411.51	412.4	2.972

2a-49	3-acetamido-	H-	4- 4-tolyl-O-	H-	382.46	383.3	2.954
2a-50	4- CH ₃ -CHCl-CO-NH-	3-acet-amido-	4- 4-tolyl-O-	H-	487.99	488.4	2.876
2a-51	4- (tert-butyl-oxy-carbonyl-amino)-	H-	4- 4-tolyl-O-	H-	440.54	441.3	3.446
2a-52	3-dimethylamino-	4-acet-amido-	4- 4-tolyl-O-	H-	425.53	426.4	2.300
2a-53	4- CH ₃ -SO ₂ -NH-	H-	4- 4-tolyl-O-	H-	418.52	419.4	2.900
2a-54	4- Et-NH-CO-NH-	H-	4- [(napht-1-yl)-N(CH ₃)]-	H-	460.58	461.4	2.254
2a-55	3-acetamido-	H-	4- [(napht-1-yl)-N(CH ₃)]-	H-	431.54	432.4	2.234
2a-56	4- CH ₃ -SO ₂ -NH-	H-	4- [(napht-1-yl)-N(CH ₃)]-	H-	467.59	468.2	2.132
2a-57	4-acetamido-	H-	4- [(napht-1-yl)-N(CH ₃)]-	H-	431.54	432.4	2.174
2a-58	4- CH ₃ -CHCl-CO-NH-	3-acet-amido-	4- Ph-CHOH-	H-	487.99	488.4	2.316
2a-59	4- (tert-butyl-oxy-carbonyl-amino)-	H-	4- 4-Cl-Ph-	4- HO-	460.96	387.1	3.234
2a-60	4- CH ₃ -CHCl-CO-NH-	3-acet-amido-	4- 4-tolyl-CH ₂ -	H-	486.02	486.4	3.182
2a-61	4- (tert-butyl-oxy-carbonyl-amino)-	H-	4- 4-tolyl-CH ₂ -	H-	438.57	439.4	3.679
2a-62	4- (tert-butyl-oxy-carbonyl-amino)-	H-	4- [4-Br-Ph-N(CH ₃)-]	H-	518.46	519.3	2.627
2a-63	4- CH ₃ -CHCl-CO-NH-	3-acet-amido-	4- 4-Cl-benzyl-	H-	506.43	506.2	3.251
2a-64	4- CH ₃ -CHCl-CO-NH-	3-acet-amido-	4- 4-Cl-Ph-O-	H-	508.41	508.3	3.028
2a-65	3-dimethylamino-	4-acet-amido-	4- 4-Cl-Ph-O-	H-	445.95	446.3	2.457

2a-66	4- CH ₃ -CHCl-CO-NH-	3-acet-amido-	4- 4-Cl-Ph-	4- HO-	508.41	490.1	2.623
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Compounds of formula (IA), where the dotted bond means a double C-C bond and A is a -CH= group:

Table 2b

No.	R ¹	R ²	R ⁵	R ⁶	MW _c	MW _m	k'
2b-1	4- Et-NH-CO-NH-	H-	4- Ph-	-	379.46	380.2	2.927
2b-2	3-acetamido-	H-	4- Ph-	-	350.42	351.2	2.899
2b-3	4- CH ₃ -CHCl-CO-NH-	3-acet-amido-	4- Ph-	-	455.95	457	2.818
2b-4	4- (tert-butyl-oxy-carbonyl-amino)-	H-	4- Ph-	-	408.50	409.3	3.418
2b-5	4- CH ₃ -SO ₂ -NH-	H-	4- Ph-	-	386.47	387.1	2.850
2b-6	4-acetamido-	H-	4- Ph-	-	350.42	351.2	2.855

5

Compounds of formula (IA), where the dotted bond means a simple C-C bond and A is an -NH- group:

Table 3a

No.	R ¹	R ²	R ⁵	R ⁶	MW _c	MW _m	k'
3a-1	4- Et-NH-CO-NH-	H-	4- 3-CF ₃ -Ph-	-	450.46	451.3	3.068
3a-2	3-acetamido-	H-	4- 3-CF ₃ -Ph-	-	421.42	422.2	3.055
3a-3	4- CH ₃ -CHCl-CO-NH-	3-acet-amido-	4- 3-CF ₃ -Ph-	-	526.95	527.2	2.980
3a-4	4- (tert-butyl-oxy-carbonyl-amino)-	H-	4- 3-CF ₃ -Ph-	-	479.50	480.3	3.535
3a-5	3-dimethylamino-	4-acet-amido-	4- 3-CF ₃ -Ph-	-	464.49	456.2	2.407
3a-6	4-acetamido-	H-	4- 3-CF ₃ -Ph-	-	421.42	422.2	3.006
3a-7	4- Et-NH-CO-NH-	H-	4- 4-Cl-Ph-	-	416.91	417.1	2.696
3a-8	3-acetamido-	H-	4- 4-Cl-Ph-	-	387.87	388.2	2.656
3a-9	4- CH ₃ -CHCl-CO-NH-	3-acet-amido-	4- 4-Cl-Ph-	-	493.39	494.3	2.598

3a-10	4- (tert-butyl-oxy-carbonyl-amino)-	H-	4- 4-Cl-Ph-	-	445.95	446.3	3.277
3a-11	4- CH ₃ -SO ₂ -NH-	H-	4- 4-Cl-Ph-	-	423.92	424.2	2.609
3a-12	4-acetamido-	H-	4- 4-Cl-Ph-	-	387.87	388.2	2.615
3a-13	4- Et-NH-CO-NH-	H-	4- Ph ₂ CH-	-	472.59	473.3	2.067
3a-14	3-acetamido-	H-	4- Ph ₂ CH-	-	443.55	444.2	2.046
3a-15	4- (tert-butyl-oxy-carbony-amino)-	H-	4- Ph ₂ CH-	-	501.63	502.3	2.611
3a-16	4- CH ₃ -SO ₂ -NH-	H-	4- Ph ₂ CH-	-	479.60	480.2	3.049
3a-17	4-acetamido-	H-	4- Ph ₂ CH-	-	443.55	444.2	1.956
3a-18	4- CH ₃ -CHCl-CO-NH-	3-acet-amido-	4- Ph ₂ CH-	-	549.07	549.2	2.035

Compounds of the formula (IA), where the dotted bond means a simple C-C bond and A is a -CH₂- group:

Table 3b

No.	R ¹ and R ² together	R ⁵	R ⁶	MW _c	MW _m	k'
3b-1	3,4- -NH-CO-NH-	4-benzyl-	H-	365.44	366.3	2.922
3b-2	3,4- -NH-N=CH-	4-benzyl-	H-	349.44	350.2	3.123
3b-3	3,4- -NH-CO-NH-	4- 4-F-benzyl-	H-	383.43	384.2	2.979
3b-4	3,4- -NH-CO-O-	4- 4-F-benzyl-	H-	384.41	385.2	3.127
3b-5	3,4- -NH-CO-O-	4- 4-F-Ph-CH ₂ CH ₂ -	H-	398.44	399.3	3.321
3b-6	3,4- -NH-N=CH-	4- [4-tolyl-N(CH ₃)-]	H-	378.48	379.5	2.029
3b-7	3,4- -NH-CO-NH-	4- 4-tolyl-CH ₂ -	H-	379.46	380.3	3.115
3b-8	3,4- -NH-N=CH-	4- 4-tolyl-CH ₂ -	H-	363.46	364.3	3.298
3b-9	3,4- -NH-CO-O-	4- [4-Br-Ph-N(CH ₃)-]	H-	460.33	461.3	2.078
3b-10	3,4- -NH-N=CH-	4- 4-Cl-benzyl-	H-	383.88	384.3	3.355
3b-11	3,4- -NH-CO-NH-	4- 4-Cl-Ph-O-	H-	401.85	402.3	2.968
3b-12	3,4- -NH-CO-O-	4- 4-Cl-Ph-O-	H-	402.84	403.3	3.098
3b-13	3,4- -NH-N=CH-	4- 4-Cl-Ph-O-	H-	385.85	386.3	3.155
3b-14	3,4- -NH-CO-NH-	4- 4-tolyl-O-	H-	381.44	382.3	2.820
3b-15	3,4- -NH-CO-O-	4- 4-tolyl-O-	H-	382.42	383.3	2.957

3b-16	3,4- -NH-N=CH-	4- 4-tolyl-O-	H-	365.44	366.3	3.015
3b-17	3,4- -NH-CO-O-	4- Ph-CHOH-	H-	382.42	383.2	2.434
3b-18	3,4- -NH-N=CH-	4- Ph-CHOH-	H-	365.44	366.2	2.467
3b-19	3,4- -NH-CO-O-	4- 4-Cl-Ph-	4- HO-	402.84	403.1	2.709
3b-20	3,4- -NH-N=CH-	4- 4-Cl-Ph-	4- HO-	385.85	386.2	2.746
3b-21	3,4- -NH-N=CH-	4- 4-F-benzyl-	H-	367.43	368.2	3.178
3b-22	3,4- -NH-CO-NH-	4- 4-F-Ph-CH ₂ -CH ₂ -	H-	397.45	398.2	3.205
3b-23	3,4- -NH-N=CH-	4- 4-F-Ph-CH ₂ -CH ₂ -	H-	381.45	382.53	3.370
3b-24	3,4- -NH-CO-O-	4- 4-tolyl-CH ₂ -	H-	380.45	381.5	3.254
3b-25	3,4- -NH-CO-O-	4- 4-Cl-benzyl-	H-	400.87	401.3	3.313

Compounds of formula (IA), where the dotted bond means a double C-C bond and A is a -CH= group:

Table 4a

No.	R ¹ and R ² together	R ⁵	R ⁶	MW _c	MW _m	k'
4a-1	3,4- -NH-CO-NH-	4- Ph-	-	349.39	350.2	2.763
4a-2	3,4- -NH-CO-O-	4- Ph-	-	350.38	351.2	2.913
4a-3	3,4- -NH-N=CH-	4- Ph-	-	333.39	334.2	2.965

5

Compounds of formula (IA), where the dotted bond means a simple C-C bond and A is an -NH- group:

Table 4b

No.	R ¹ and R ² together	R ⁵	R ⁶	MW _c	MW _m	k'
4b-1	3,4- -NH-CO-O-	4- 3-CF ₃ -Ph-	-	421.38	422.1	3.065
4b-2	3,4- -NH-N=CH-	4- 3-CF ₃ -Ph-	-	404.40	405.2	3.127
4b-3	3,4- -NH-CO-O-	4- Ph ₂ CH-	-	443.51	444.2	1.976

10

Example 2**Preparation of pharmaceutical compositions:****a) Tablets:**

0.01-50 % of active ingredient selected from the new aryloxy acetic acid amide derivatives of formula (I), 15-50 % of lactose, 15-50 % of potato starch, 5-15 % of polyvinyl pyrrolidone, 1-5 % of talc, 0.01-3 % of magnesium stearate, 1-3 % of colloid silicon dioxide and

15

2-7 % of ultraamylopectin are mixed, then are granulated by wet granulation and pressed to tablets.

b) Dragées, filmcoated tablets:

The tablets made according to the method described above are coated by a layer consisting of entero- or gastrosolvent film, or of sugar and talc. The dragées are polished by a mixture of beeswax and carnuba wax.

c) Capsules:

0.01-50 % of active ingredient selected from the new aryloxy acetic acid amide derivatives of formula (I), 1-5 % of sodium lauryl sulfate, 15-50 % of starch, 15-50 % of lactose, 1-3 % of colloid silicon dioxide and 0.01-3 % of magnesium stearate are thoroughly mixed, the mixture is passed through a sieve and filled in hard gelatin capsules.

d) Suspensions:

Ingredients: 0.01-15 % of active ingredient selected from the new aryloxy acetic acid amide derivatives of formula (I), 0.1-2 % of sodium hydroxide, 0.1-3 % of citric acid, 0.05-0.2 % of nipagin (sodium methyl 4-hydroxybenzoate), 0.005-0.02 % of nipasol, 0.01-0.5 % of carbopol (polyacrylic acid), 0.1-5 % of 96 % ethanol, 0.1-1 % of flavoring agent, 20-70 % of sorbitol (70 % aqueous solution) and 30-50 % of distilled water.

To solution of nipagin and citric acid in 20 ml of distilled water, carbopol is added in small portions under vigorous stirring, and the solution is left to stand for 10-12 h. Then the sodium hydroxide in 1 ml of distilled water, the aqueous solution of sorbitol and finally the ethanolic raspberry flavor are added with stirring. To this carrier the active ingredient is added in small portions and suspended with an immersing homogenizator. Finally the suspension is filled up to the desired final volume with distilled water and the suspension syrup is passed through a colloid milling equipment.

e) Suppositories:

For each suppository 0.01-15% of active ingredient selected from the new aryloxy acetic acid amide derivatives of formula (I) and 1-20% of lactose are thoroughly mixed, then 50-95% of adeps pro suppository (for example Witepsol 4) is melted, cooled to 35 °C and the mixture of active ingredient and lactose is mixed in it with homogenizator. The obtained mixture is moulded in cooled forms.

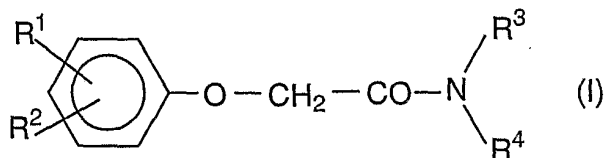
f) Lyophilized powder ampoule compositions:

A 5 % solution of mannitol or lactose is made with bidistilled water for injection use, and the solution is filtered so as to have sterile solution. A 0.01-5 % solution of the active ingredient

selected from the new aryloxy acetic acid amide derivatives of formula (I) is also made with bidistilled water for injection use, and this solution is filtered so as to have sterile solution. These two solutions are mixed under aseptic conditions, filled in 1 ml portions into ampoules, the content of the ampoules is lyophilized, and the ampoules are sealed under nitrogen. The contents
5 of the ampoules are dissolved in sterile water or 0.9 % (physiological) sterile aqueous sodium chloride solution before administration.

What we claim is:

1. New aryloxy acetic acid amide derivatives of formula (I)



where

- 5 R^1 and R^2 are the same or different and can be hydrogen atom or
 C_{1-4} alkanoylamido group optionally substituted by halogen atom or
 C_{1-4} alkyl-sulfonylamido group or
 N' -(C_{1-4} alkyl)-ureido group
 C_{1-6} alkoxy-carbonyl-amido or
10 di-(C_{1-4} alkyl)-amino group
with the proviso that only one of them can be hydrogen atom, or
 R^1 and R^2 form together a -NH-CO-NH-, -NH-N=CH- or -NH-CO-O- chain attached to two
neighbouring carbon atoms of the benzyl group,
 R^3 and R^4 mean the same or different C_{1-4} alkyl groups which are substituted by phenyl group,
15 or
 R^3 and R^4 mean together a C_{4-6} alkylene chain which can be interrupted optionally by a nitrogen
atom and which can contain a C-C double bond and which C_{4-6} alkylene chain can
substituted by one or two substituents from the following
hydroxy group,
20 phenyl or phenoxy group optionally substituted by a C_{1-4} alkyl or trifluoro methyl
group,
=CH-phenyl group which can be substituted by halogen atom or C_{1-4} alkyl group,
 C_{1-4} alkyl group optionally substituted by hydroxy group and one or two phenyl
groups which can be substituted by halogen atom or C_{1-4} alkyl group,
25 C_{1-4} alkyl amino group which is substituted by a phenyl or naphthyl group which can
be substituted optionally by a halogen atom or a C_{1-4} alkyl group,
as well as their salts formed with organic or inorganic acids or bases and solvates of these
compounds.

2. Compounds of formula (I) as claimed in claim 1, where R^3 and R^4 mean the same or different C_{1-4} alkyl groups which are substituted by phenyl group and R^1 and R^2 have the same meaning as defined in claim 1.

3. Compounds of formula (I) as claimed in claim 1, where R^3 and R^4 mean together a C_{4-6} alkylene chain which can be interrupted optionally by a nitrogen atom and which can contain a C-C double bond and which C_{4-6} alkylene chain can substituted by one or two substituents from the following

hydroxy group,

phenyl or phenoxy group optionally substituted by a C_{1-4} alkyl or trifluoro methyl group,

=CH-phenyl group which can be substituted by halogen atom or C_{1-4} alkyl group,

C_{1-4} alkyl group optionally substituted by hydroxy group and one or two phenyl groups which can be substituted by halogen atom or C_{1-4} alkyl group,

C_{1-4} alkyl amino group which is substituted by a phenyl or naphthyl group which can be substituted optionally by a halogen atom or a C_{1-4} alkyl group, and

R^1 and R^2 have the same meaning as defined in claim 1.

4. Compounds of formula (I) as claimed in claim 1, where

R^1 and R^2 are the same or different and can be hydrogen atom or

C_{1-4} alkanoylamido group optionally by halogen atom substituted or

C_{1-4} alkyl-sulfonylamido group or

N'-(C_{1-4} alkyl)-ureido group

C_{1-6} alkoxy-carbonyl-amido or

di-(C_{1-4} alkyl)-amino group

with the proviso that only one of them can be hydrogen atom, and

R^3 and R^4 have the same meaning as defined in claim 1.

5. Compounds of formula (I) as claimed in claim 1, where

R^1 and R^2 form together a -NH-CO-NH-, -NH-N=CH- or -NH-CO-O- chain attached to two neighbouring carbon atoms of the phenyl group, and

R^3 and R^4 have the same meaning as defined in claim 1.

6. A member of the following group of compounds of formula (I) as claimed in claim

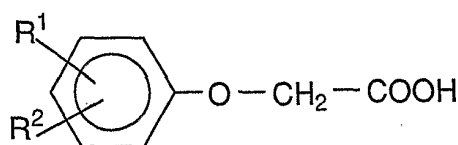
5-{2-[4-(4-methyl-benzyl)-piperidin-1-yl]-2-oxo-ethoxy}-1,3-dihydro-benzoimidazol-2-one,
N-(4-{2-[4-(4-methyl-benzyl)-piperidin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonamide,

N-(4-{2-[4-(4-chloro-benzyl)-piperidin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonamide,
 5-{2-[4-(4-chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethoxy}-1,3-dihydro-benzoimidazol-2-one
 and
 5-{2-[4-(4-chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethoxy}-3H-benzooxazol-2-one.

5 7. Pharmaceutical compositions having an NR2B subtype specific NMDA antagonist effect, **characterized by** comprising a biologically effective dose of a new aryloxy acetic acid amide derivative of formula (I) – wherein the meaning of R^1 , R^2 , R^3 and R^4 are as defined in claim 1 – and/or pharmaceutically acceptable salts thereof formed with acids or bases as active ingredient and carriers, filling materials and the like usually applied in
 10 pharmaceuticals.

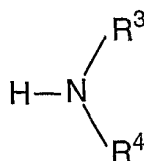
8. Process for preparing of new aryloxy acetic acid amide derivatives of formula (I) – wherein the meaning of R^1 , R^2 , R^3 and R^4 are as defined in claim 1 – and/or their salts formed with organic or inorganic acids or bases and solvates of these compounds
characterized by reacting an aryloxy acetic acid of formula (II)

15



(II)

or a reactive derivative of it - where R^1 and R^2 have the same meaning as defined in claim 1 - with a secondary amine of formula (III)



(III)

20 - where R^3 and R^4 have the same meaning as defined in claim 1 - and

the obtained compounds of formula (I) - where R^1 , R^2 , R^3 and R^4 are as defined in claim 1 - are transformed in given case into an other compound of formula (I) by introducing further substituents and/or modifying and/or removing the existing ones, and/or by forming salts with acids and/or bases and/or by liberating the new aryloxy acetic acid amide derivative of formula

(I) from the obtained salts by treating with a base and/or acid and/or by forming solvates from them.

9. Process as claimed in claim 8, **characterized by** in situ forming the reactive derivative of the aryloxy acetic acid of formula (II) - where R^1 and R^2 have the same meaning as defined in claim 1 - by using of a carbodiimide.

10. Process as claimed in claim 8, **characterized by** using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) as carbodiimide.

11. Process for manufacturing pharmaceutical compositions having NR2B selective NMDA receptor antagonist effect, **characterized by** mixing an aryloxy acetic acid amide derivative of formula (I) - wherein the meaning of R^1 , R^2 , R^3 and R^4 are as defined in claim 1 - or the pharmaceutically acceptable salts thereof as active ingredient and auxiliary materials, which are commonly used in practice, such as carriers, excipients, diluents, stabilizers, wetting or emulsifying agents, pH- and osmotic pressure-influencing, flavoring or aromatizing, as well as formulation-promoting or formulation-providing additives.

12. Method of treatment and alleviation of symptoms of the following diseases of mammals - including human - chronic neurodegenerative disorders, such as stroke, Alzheimer's disease, Parkinson's disease, Huntington's disease, injury of spinal cord, epilepsy, anxiety, depression, cerebral ischemia of any origin, muscular spasm, multiinfarct dementia, injury of brain, pain (e.g. posttraumatic or postoperative) and chronic pain states, such as neuropathic pain or cancer related pain, migraine, human immunodeficiency virus (HIV) related neuronal injury, hypoglycemia, amyotrophic lateral sclerosis (ALS), bacterial sclerosis, macula degeneration, degenerative disorders of the retina (e.g. CMV retinitis) asthma, tinnitus, aminoglycoside antibiotic-induced hearing loss, bacterial and viral infections, to decrease tolerance and/or dependence to drugs and alcohol, and for treatment of withdrawal syndrome of drugs and alcohol, psychosis, bladder incontinence, **characterized by** administering effective amount/amounts of an aryloxy acetic acid amide derivative of formula (I) - wherein the meaning of R^1 , R^2 , R^3 and R^4 are as defined in claim 1 - and/or pharmaceutically acceptable salts thereof formed with acids or bases as active ingredient as such or suitably in the form of pharmaceutical composition manufactured with known auxiliaries usually applied in pharmaceuticals to a mammal - including human - to be treated.

13. Use of an aryloxy acetic acid amide derivative of formula (I) - wherein the meaning of R^1 , R^2 , R^3 and R^4 are as defined in claim 1 - and/or optical antipodes or racemates and/or pharmaceutically acceptable salts thereof for the preparation of a pharmaceutical for the

treatment and alleviation of symptoms of the following diseases in a mammals, including humans: chronic neurodegenerative disorders, such as stroke, Alzheimer's disease, Parkinson's disease, Huntington's disease, injury of spinal cord, epilepsy, anxiety, depression, cerebral ischemia of any origin, muscular spasm, multiinfarct dementia, injury of brain, pain (e.g. posttraumatic or postoperative) and chronic pain states, such as neuropathic pain or cancer related pain, migraine, human immunodeficiency virus (HIV) related neuronal injury, hypoglycemia, amyotrophic lateral sclerosis (ALS), bacterial sclerosis, macula degeneration, degenerative disorders of the retina (e.g. CMV retinitis) asthma, tinnitus, aminoglycoside antibiotic-induced hearing loss, bacterial and viral infections, to decrease tolerance and/or dependence to drugs and alcohol, and for treatment of withdrawal syndrome of drugs and alcohol, psychosis, bladder incontinence.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/HU2005/000081

A. CLASSIFICATION OF SUBJECT MATTER

C07C235/34 C07D211/08 C07D235/06 C07D263/56 A61K31/16
A61K31/18 A61K31/445 A61K31/4184

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE BEILSTEIN Beilstein Institut zur Foerderung der Chemischen Wissenschaften; XP002356754 Database accession no. BRN 851696 abstract & POPESCU: FARMACIA (BUCHAREST), vol. 15, 1967, pages 661-663, -----	1-11,13
X	FR 1 571 198 A (C.H. BOEHRINGER SOHN) 13 June 1969 (1969-06-13) page 1, compound of general formula (I); claims -----	1-11,13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

30 November 2005

Date of mailing of the international search report

20/12/2005

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Authorized officer

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU2005/000081

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 12 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/HU2005/000081

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 1571198	A	13-06-1969	FR 8297 M
			16-11-1970