PIPERIDINE DERIVATIVES AS NMDA RECEPTOR ANTAGONISTS

The invention relates to new carboxylic acid amide derivatives which are antagonists of NMDA receptor or are intermediates for preparing thereof.

Background of the invention.

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 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 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 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 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 radioligands, such as [^{125}I]-ifenprodil [J.Neurochem., **61**, 120-126 (1993)] or [^{3}H]-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.

Close stucture analogs of the carboxylic acid amide derivatives of formula (I) are known from the literature.

The Florida Center for Heterocyclic Compounds [Department of Chemistry, University of Florida, P O Box 117200, Gainesville, FL, 32611-7200, USA] provides milligram quantities of three compounds of formula (I) for biological testing: N-(4-bromophenyl)-4-(phenylmethyl)-1-piperidineacetamide, 4-[[oxo[4-(phenylmethyl)-1-piperidinyl]acetyl]amino]benzoic acid and 4-[[oxo[4-(phenylmethyl)-1-piperidinyl]acetyl]amino]benzoic acid ethyl ester.

Oxo-ethylamino derivatives are described as intermediates for thrombin inhibitors [Bioorg. Med. Chem. Letters, 9, 925. (1999)]. The publication does not describe NMDA receptor antagonist effect.

N-(4-Benzoylphenyl)-4-(phenylmethyl)-1-piperidineacetamide is mentioned in patent No. US 6,048,900 as selective neuropeptide Y receptor antagonist.

N-(2-Formyl-6-methylphenyl)-4-(phenylmethyl-1-piperidineacetamide is described in patent No. AU 639529 as intermediate for carbostyril derivative which is useful as antiarrhythmics.

Aminoacetarylides are also known [Rev. Chim. (Bucharest), 33(7), 601. (1982); CA 97:174467a] as local anesthetic and antifibrillatory agents.

Piperidine derivatives and analogues substituted with phenols or phenol equivalents having NR2B selective NMDA antagonist activity are described in international patent applications WO90/14087, WO90/14088, WO97/23202, WO97/23214, WO97/23215, WO97/23216, WO97/23458, WO99/21539, WO2000/25109, EP648,744 and in US 5,436,255. Compounds containing 2-benzoxazolinone substructure with the same biological activity are described in international patent applications WO98/18793 and WO2000/00197. Other NR2B selective NMDA antagonists having condensed heterocyclic structures are described in WO2001/30330, WO2001/32171, WO2001/32174, WO2001/32177, WO2001/32179, WO2001/32615, WO2001/32634.

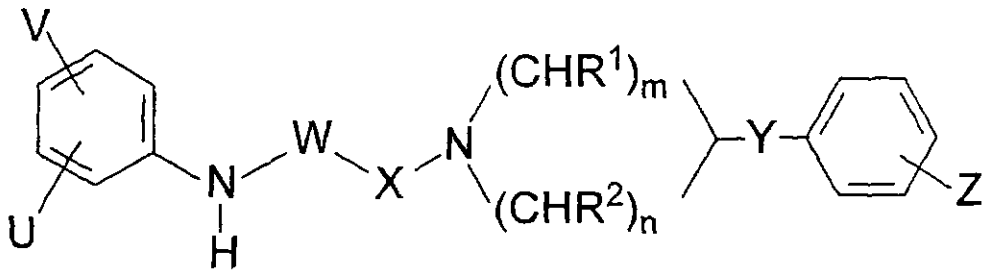
However, there continues to be a need for novel NMDA antagonists that target the NR2B receptor.

Summary of the invention

Surprisingly it was found that the new carboxylic 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.

Detailed description of the invention

The present invention relates therefore first to new carboxylic acid amide derivatives of formula (I)



(I)

- wherein

V and U independently are hydrogen or halogen atom, hydroxyl, cyano, nitro, amino, C_1-C_4 alkylamino optionally substituted by a halogen atom or halogen atoms, arylamino optionally substituted by a halogen atom or halogen atoms, aralkylamino optionally substituted by a halogen atom or halogen atoms, C_1-C_4 alkylsulfonamido optionally substituted by a halogen atom or halogen atoms, C_1-C_4 alkanoylamido optionally substituted by a halogen atom or halogen atoms, arylsulfonamido, C_1-C_4 alkylsulfonyloxy, carboxyl, trifluoromethyl, trifluoromethoxy, C_1-C_4 alkyl-SO_2-NH-CH_2-, NH_2-$(CH_2)_{1-4}$-SO_2-NH-, NH_2-$(CH_2)_{1-4}$-(CO)-NH-, sulfamoyl [NH_2-SO_2-], formyl [-CHO], amino-methyl [-CH_2-NH_2], hydroxymethyl, C_1-C_4 alkyl, C_1-C_4 alkoxymethyl, halogenmethyl, tetrazolyl group, or C_1-C_4 alkoxy, C_1-C_4 alkoxycarbonyl, C_1-C_6 alkanoyloxy, phenyl or C_1-C_4 alkoxy groups, optionally substituted by amino group, or

the neighboring V and U groups in given case together with one or more identical or different additional hetero atom and -CH= and/or -CH_2- groups can form an optionally substituted 4-7 membered homo- or heterocyclic ring, preferably morpholine, pyrrole, pyrrolidine, oxo- or thioxo-pyrrolidine, pyrazole, pyrazolidine, imidazole,

imidazolidine, oxo- or thioxo-imidazole or imidazolidine, 1,4-oxazine, oxazole, oxazolidine, oxo- or thioxo-oxazolidine, or 3-oxo-1,4-oxazine ring,

W and X independently are -CO-, -CH_2- or -CH(-alkyl)- groups - wherein alkyl is a C_1-C_4 alkyl group groups - with the restriction, that the meaning of W and X can not be methylene at the same time

Y is oxygen atom, as well as C_1-C_4 alkylene, C_1-C_4 alkynylene, cycloalkylene, aminocarbonyl, -NH-, -N(alkyl)-, -CH_2O-, -CH(OH)-, -OCH_2- group, - wherein alkyl is a C_1-C_4 alkyl group -,

Z is hydrogen or halogen atom, nitro, amino, C_1-C_4 alkyl, C_1-C_4 alkoxy, cyano, trifluoromethyl, hydroxyl or carboxyl group,

R^1 and R^2 independently are hydrogen atom or alkyl group, or R^1 and R^2 together form an optionally substituted C_1-C_3 bridge and

n and m independently are 0-3, with the restriction, that n and m can not be 0 at the same time,

and optical antipodes or racemates and/or pharmaceutically acceptable salts thereof formed with acids and bases with the proviso that

when Z means hydrogen atom, Y means -CH_2- group, both of m and n mean 2, both of R^1 and R^2 mean hydrogen atom, W means -CO- group, X means -CH_2- group and V means hydrogen atom, then the meaning of U is other than a 4-bromo substituent and

when Z means hydrogen atom, Y means -CH_2- group, both of m and n mean 2, both of R^1 and R^2 mean hydrogen atom, both of W and X mean -CO- group and V means hydrogen atom, then the meaning of U is other than a 4-carboxyl or 4-etoxycarbonyl substituent.

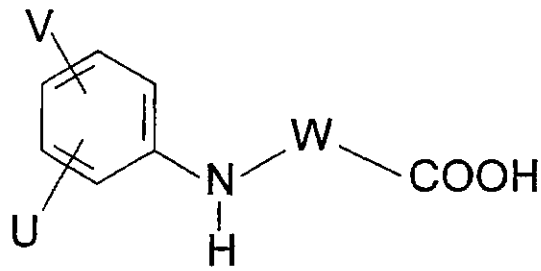
Furthermore objects of the present invention are the pharmaceutical compositions containing carboxylic acid amide compounds of formula (I) or optical antipodes or racemates or the salts thereof as active ingredients.

A further object of the invention are the processes for producing of carboxylic acid amide compounds of formula (I), and the pharmaceutical manufacture of medicaments containing these compounds, as well as the process of treatments with these compounds, which means administering to a mammal to be treated - including human - effective amount/amounts of compounds of formula (I) of the present invention as such or as medicament.

The new carboxylic acid amide derivatives of formula (I) of the present invention are highly effective and selective antagonists of NMDA receptor, and moreover most of the compounds are selective antagonist of NR2B subtype of NMDA receptor.

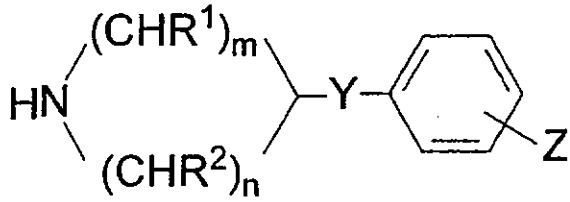
According to the invention the carboxylic acid amide compounds of formula (I) can be prepared by the following processes

a.) for producing of compounds of formula (I) having -CO- group in place of X - wherein the meaning of R^1, R^2, Y, Z, U, V, W, n and m are as given before for the formula of (I) - a carboxylic acid of formula (II)



(II)

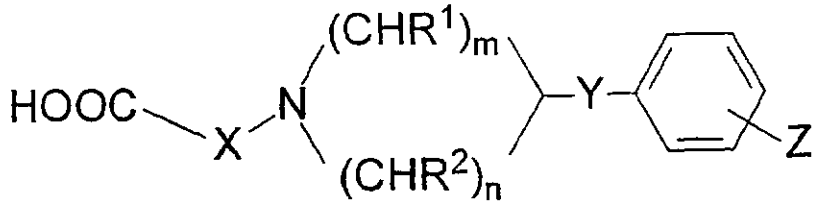
- wherein the meaning of U, V and W are as given for the formula of (I) - or a reactive derivative of it is reacted with an amine of formula (III)



(III)

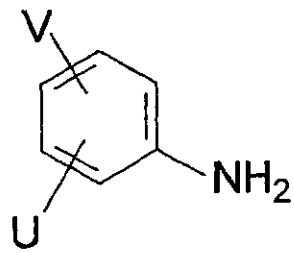
- wherein the meaning of R^1, R^2, Y, Z, n and m are as given before for the formula of (I) - , or

b.) for producing of compounds of formula (I) having -CO- group in place of W - wherein the meaning of R^1, R^2, Y, Z, U, V, X, n and m are as given before for the formula of (I) - a carboxylic acid of formula (IV)



(IV)

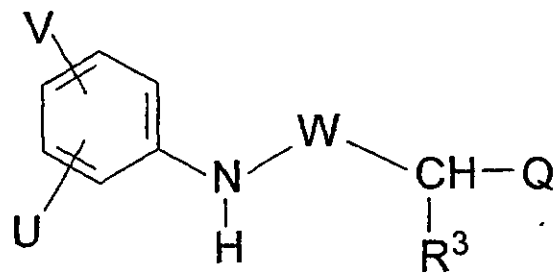
- wherein the meaning of X, R^1, R^2, Y, Z, n and m are as described above for the formula of (I) - or a reactive derivative of it is reacted with an amine of formula (V)



(V)

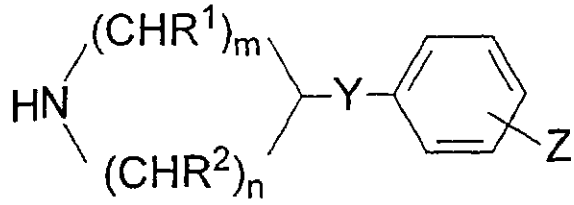
- wherein the meaning of U and V are as given before for the formula of (I) -, or

c.) for producing of compounds of formula (I) having $-CH_2-$ or -CH(-alkyl)- group in place of X - wherein alkyl is a C_1-C_4 alkyl group and the meaning of R^1, R^2, Y, Z, U, V, W, n and m are as given before for the formula of (I) - a halogene derivative of a compound of formula (VI)



(VI)

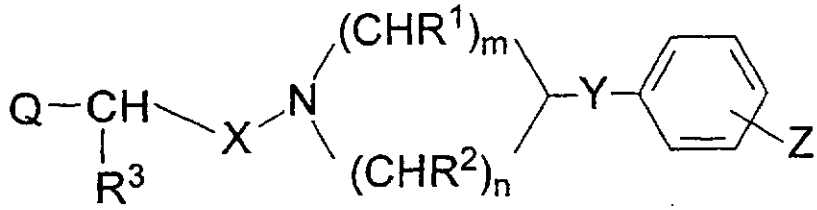
- wherein the meaning of Q is halogen atom, R^3 is hydrogen atom or a C_1-C_4 alkyl group and U, V and W are as described above for the formula of (I) - is reacted with an amine of formula (III)



(III)

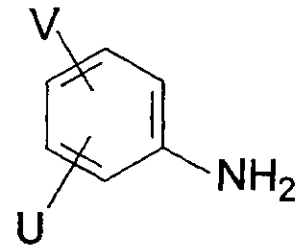
- wherein the meaning of R^1, R^2, Y, Z, n and m are as given before for the formula of (I) -, or

d.) for producing of compounds of formula (I) having $-CH_2-$ or -CH(-alkyl)- group in place of W - wherein alkyl is a C_1-C_4 alkyl group and the meaning of R^1, R^2, Y, Z, U, V, X, n and m are as given before for the formula of (I) - a halogene derivative of a compound of formula (VII)



(VII)

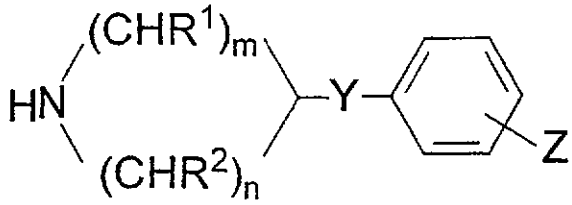
- wherein the meaning of Q is halogen atom, R^3 is hydrogen atom or a C_1-C_4 alkyl group and X, R^1, R^2, Y, Z, n and m are as described above for the formula of (I) - is reacted with an amine of formula (V)



(V)

- wherein the meaning of U and V are as given before for the formula of (I) -, or

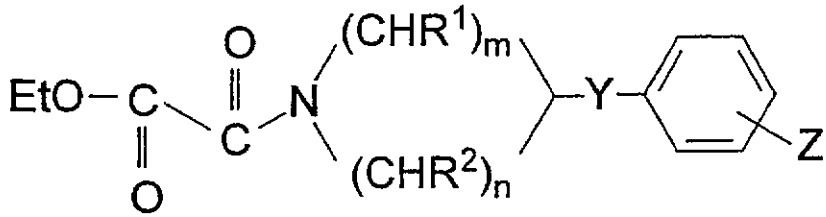
e.) for producing compound of formula (I), where X mean -CO- group and R^1, R^2, Y, Z, U, V, n and m are as defined for the formula (I), a secondary amine of formula (III)



(III)

- where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I) - is reacted with ethyl oxalylchloride in the presence of solid-supported base in dichloromethane,

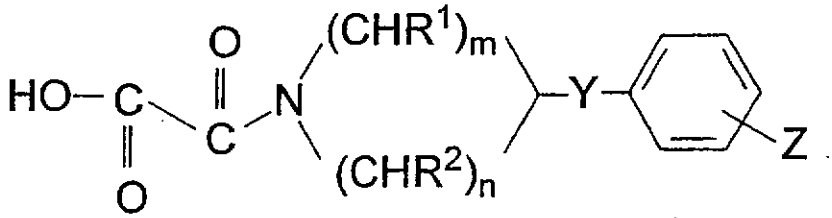
the obtained ester compound of formula (VIII)



(VIII)

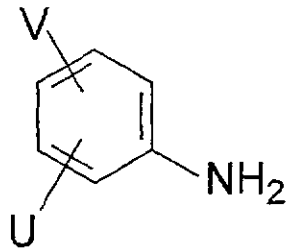
- where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I) - is saponified with a strongly basic ion exchange resin in ethanol and

the obtained oxalamid acid of formula (IX)



(IX)

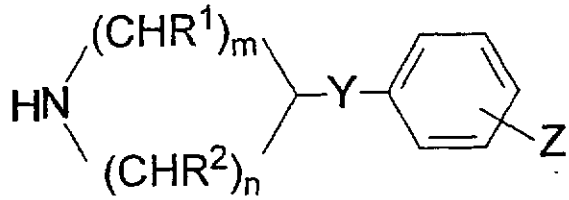
where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I) is reacted with an amide of formula (V)



(V)

- wherein the meaning of U and V are as given before for the formula of (I) - in dichloromethan/dimethylformamide mixture in the presence of 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide, or

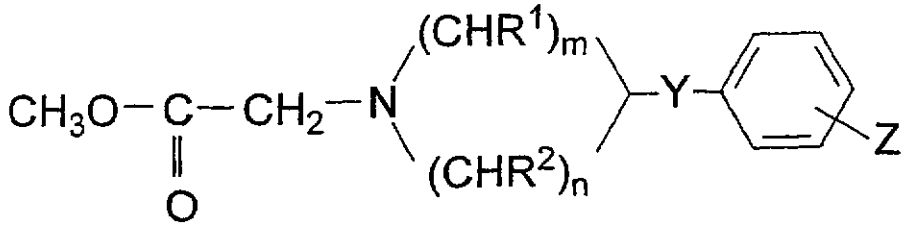
f.) for producing compound of formula (I), where X mean $-CH_2-$ group and R^1, R^2, Y, Z, U, V, n and m are as defined for the formula (I), a secondary amine of formula (III)



(III)

- where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I) - is reacted with methyl bromoacetate in the presence of potassium carbonate in dimethylformamide,

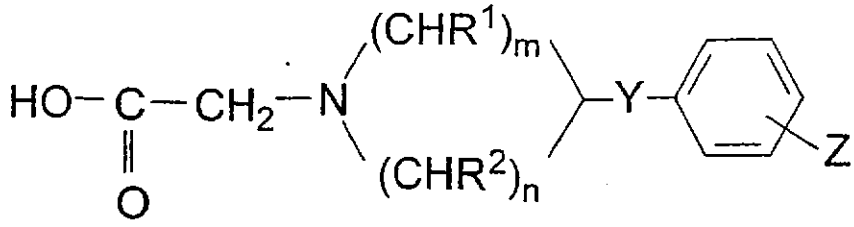
the obtained ester compound of formula (X)



(X)

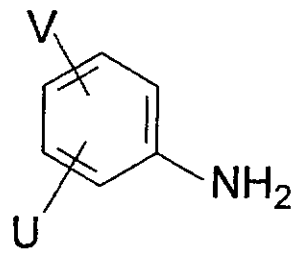
where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I) is saponified with a strongly basic ion exchange resin in ethanol and

the obtained substituted glycine of formula (XI)



(XI)

where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I) is reacted with an amide of formula (V)



(V)

- wherein the meaning of U and V are as given before for the formula of (I) - in dichloromethan/dimethylformamide mixture in presence of 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide,

and the obtained compounds of formula (I) - where R^1, R^2, Y, Z, U, V, X, W, n and m are as defined above - in given case are transformed 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 liberating the carboxylic acid amide derivative of formula (I) from the obtained acid addition salts by treatment with a base and/or the free carboxylic acid amide derivative of formula (I) can be transformed into a salt by treatment with a base and/or are resolved into their optical antipodes.

The amide bond formation is preferably carried out by preparing an active derivative from a carboxylic acid of formula (II) or (IV) which is reacted with an amine of formula (III) or (V) preferably in the presence of a base.

The transformation of a carboxylic acid into an active derivative can be carried out in situ during the amide bond formation in a proper solvent (for example dimethylformamide, acetonitrile, chlorinated hydrocarbons or hydrocarbons). The active derivatives can be acid chlorides (for example prepared from carboxylic acid with thionyl chloride), mixed anhydrides

(for example prepared from carboxylic acid with isobutyl chloroformate in the presence of a base, e.g. triethylamine), active esters (for example prepared from carboxylic acid with hydroxybenztriazol and dicyclohexyl-carbodiimide or O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) in the presence of a base e.g. triethylamine), acid azides (for example prepared from carboxylic acid hydrazide). The active derivatives can be prepared between room temperature and 0 °C. A proper amine of formula (III) or (V) is added as base or as a salt formed with inorganic acid to the so obtained solution or suspension in the presence of a base, for example triethylamine, needed for the liberation of the amine. The condensation reactions are followed by thin layer chromatography. The necessary reaction time is 6-20 h. The work-up of the reaction mixture can be carried out by different methods.

The amide bond formation is preferably carried out by refluxing in a proper solvent an amine of formula (III) or (V) with a halogen compound of formula (IV) or (VII) in the presence of an organic base (for example triethylamine, pyridine, piperidine) or an inorganic base (for example sodium carbonate or potassium carbonate) and sodium iodide. The proper solvent can be an aprotic solvent (for example toluene, chlorinated hydrocarbons) or a dipolar aprotic solvent (for example keton, acetonitrile or dimethylformamide). The reactions are followed by thin layer chromatography. The necessary reaction time is 20-50 h. The work-up of the reaction mixture also can be carried out by different methods.

When the reaction mixture is a suspension, the precipitate is filtered off, washed with water and/or with an organic solvent and recrystallized from a proper solvent to give the pure product. If the crystallization does not lead to the pure product, then column chromatography can be used for the purification of it. The column chromatography is carried out on normal phase using Kieselgel 60 as adsorbent and different solvent systems, e.g. toluene/methanol, chloroform/methanol or toluene/acetone, as eluents. If the reaction mixture is a solution at the end of the acylation or alkylation, it is concentrated, and the residue is crystallized or purified by column chromatography as described above. The structure of the products are determined by IR, NMR and mass spectrometry.

The obtained carboxylic acid amide derivatives of formula (I) – independently from the method of preparation – in given case can be transformed 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 liberating the carboxylic acid amide derivative of formula (I)

from the obtained acid addition salts by treatment with a base and/or the free carboxylic acid amide derivative of formula (I) can be transformed into a salt by treatment with a base.

For example cleaving the methyl and benzyl groups from methoxy and benzyloxy groups, which stands for U,V and Z, leads to phenol derivatives. The removal of the benzyl group can be carried out for example with catalytic hydrogenation or with hydrogen bromide in acetic acid solution, the cleavage of methyl group can be carried out with boron tribromide in dichloromethane solution. The compounds of formula (I) containing free phenolic hydroxy group can be transformed into acyloxy or sulfoxy derivatives with different acylating or sulfonylating agents. The reactions are carried out at room temperature in chlorinated hydrocarbons using acid chloride or acid anhydride as acylating agent in the presence of a base (for example triethylamine or sodium carbonate). The carboxylic acid amide derivatives of formula (I) containing a nitro group (I) can be transformed into amines by catalytic hydrogenation and the amines can be further reacted to give acid amides as described for the acylation of phenolic hydroxy groups. Free hydroxy groups can be esterified by acid anhydrides or acid halogenides in the presence of a base.

The carboxylic acids of formula (II) or (IV), the primary or secondary amines of formula (III) or (V) and the halogene compounds of formula (VI) or (VII) are either commercially available or can be synthesized by different known methods. The syntheses of some commercially not available carboxylic acids of formula (II) or (IV) or halogen compounds of (VI) or (VII) are described in the Examples. Following these procedures the other commercially not available carboxylic acids of formula (II) or (IV) or halogen compounds of formula (VI) or (VII) can also be prepared.

Experimental protocols

Assessing the functional NMDA antagonist potency of compounds in primary cultures of rat cortical neurons based on measuring the intracellular calcium concentration using a fluorimeter plate reader

It is known that during postnatal development the subunit composition of neuronal NMDA receptors is changing. Similar change has been detected in neuronal cell cultures [Eur. J. Neurosci., **10**, 1704-1715 (1998)]. According to data in the literature and to our own immunocytochemical examinations neuronal cells cultured for 4-7 days *in vitro* predominantly express the NR2B subunit, together with NR1 subunit. Therefore, functional test of NMDA antagonism in these cells reflects mainly an action on NR2B subunit containing receptors. Since

NMDA receptors are known to be permeable to calcium ions upon excitation, the extent of NMDA receptor activation, and its inhibition by functional antagonists can be characterised by measuring the rise in the intracellular calcium concentration following agonist (NMDA) application onto the cells. Since there is very high sequence homology between rat and human NMDA receptors (99, 95, 97 % for NR1, NR2A, and NR2B subunits, respectively), it is believed that there is little, if any, difference in their pharmacological sensitivity. Hence, results obtained with (cloned or native) rat NMDA receptors may be well extrapolated to the human ones.

The intracellular calcium measurements are carried out on primary neocortical cell cultures derived from 17 day old Charles River rat embryos [for the details on the preparation of neocortical cell culture see Johnson, M.I.; Bunge, R.P. (1992): Primary cell cultures of peripheral and central neurons and glia. In: Protocols for Neural Cell Culture, eds: Fedoroff, S.; Richardson A., The Humana Press Inc., 13-38.] After isolation, the cells are plated onto standard 96-well microplates and the cultures are maintained in an atmosphere of 95 % air-5 % CO_2 at 37 °C until testing.

The cultures are used for the intracellular calcium measurements after 4-7 days in vitro. The cells are loaded with a fluorescent Ca^{2+}-sensitive dye, Fluo-4/AM (2-2.5 μM) prior to testing. Loading is stopped by washing twice with the solution used also during the measurement (140 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 5 mM HEPES [4-(2-hydroxyethyl)-1-piperazineethane-sulfonic acid], 5 mM HEPES-Na, 20 mM glucose, 10 μM glycine, pH=7.4). Then the test compound dissolved in the above solution (90 μl/well) is added. Intracellular calcium measurements are carried out with a plate reader fluorimeter. A rise is induced by application of 40 μM NMDA in Fluo-4-fluorescence that reflects the intracellular calcium concentration. Inhibitory potency of the test compound is assessed by measuring the reduction in the calcium elevation in the presence of different concentrations of the compound. After the measurement, a standard calibration procedure [Meth. Cell. Biol., 40, 155-181 (1994)] is applied to convert the fluorescence data to calcium concentration values.

Inhibitory potency of a compound at a single concentration point is expressed as percent inhibition of the control NMDA response. Sigmoidal concentration-inhibition curves are fitted over the data and IC_{50} values are defined as the concentration that produces half of the maximal inhibition that could be achieved with the compound. Mean IC_{50} values are derived from at least three independent experiments.

Determining binding of compounds to NR2B subunit by [^{3}H]-Ro 25.6981 binding assay

The method is essentially similar to that described by Mutel et al. [J. Neurochem., **70**, 2147-2155 (1998)] except for incubation temperature and radioligand concentration. Briefly, membranes are isolated from the forebrain of male Wistar rats. They are incubated in the presence and absence of test compound for 2 h at room temperature. Non-specific binding is determined using 10 μM Ro-25,6981, and is typically less than 7% of the total binding. The applied radioligand (^{3}H-Ro-25,6981) concentration is 4 nM. IC_{50} values (50 % inhibitory concentrations) are determined from sigmoidal fits plotted over concentration-displacement curves.

The biological activity of the compounds

IC_{50} values for selected examples of compounds of this invention in the functional NMDA antagonism and in the binding tests are listed in Table 1 and compared to those determined for the most potent known reference compounds.

The compounds of this invention exhibit IC_{50} values of less than 50 μM in the functional NMDA antagonism and in the binding tests. Thus the compounds and pharmaceutical compositions of this invention are NR2B subtype specific NMDA antagonists. Some of the compounds have superior potency compared to the known reference compounds (see Table 1).

Table 1

NMDA antagonist/binding activity of compounds on native neurons/neuronal membranes from rats

ID code of compound	NMDA IC_{50} [μM]	Ro-binding IC_{50} [μM]	Code of reference compound	NMDA IC_{50} [μM]	Ro-binding IC_{50} [μM]
70001623	0.0007	0.0047	CI-1041	0.0066	0.004
70001824	0.0014	0.0044	Co-101244	0.023	0.0033
70001861	0.0024	0.0055	EMD 95885	0.035	0.0072
70001620	0.0032	0.018	CP 101,606	0.041	0.0084
70001825	0.006	0.0017	Co-111103	0.060	0.0084
70001863	0.048	0.091	Ro 25.6981	0.159	0.0059
70001844	0.113	0.214	ifenprodil	0.483	0.096
70001712	0.164	0.029			
70001843	0.533	0.972			
70001990	1.01	0.614			

70001894	1.33	0.121
70001759	4.71	>30

NMDA IC_{50}: IC_{50} determined by the intracellular Ca^{2+}-concentartion assay on cortical neurons

Ro-binding IC_{50}: IC_{50} determined by the [^{3}H]-Ro 25,6981 binding assay on rat cerebral membranes

The reference compounds are as follows:

CI-1041: 6-{2-[4-(4-fluoro-benzyl)-piperidin-1-yl]-ethanesulfinyl}-3*H*-benzooxazol-2-one

Co 101244: 1-[2-(4-hydroxyphenoxy)ethyl]-4-hydroxy-4-(4-methylbenzyl)piperidine

EMD 95885: 6-[3-(4-fluorobenzyl)piperidine-1-yl]propionyl]-2,3-dihydro-benzoxazol-2-on

CP-101,606: (1S,2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidine-1-yl)-1-propanol

Co-111103: 1-[2-(4-hydroxyphenoxy)ethyl]-4-(4-fluorobenzyl)piperidine

Ro 256981: R-(R*,S*)-1-(4-hydroxyphenyl)-2-methyl-3-[4-(phenylmethyl)piperidin-1-yl]-1-propanol.

Ifenprodil: *erythro*-2-(4-benzylpiperidino)-1-(4-hydroxyphenyl)-1-propanol

Mouse formalin test for measurement in vivo efficacy

Injection of diluted formalin into the hind paw of rats or mouse is known to elicit a biphasic pain related behaviour measured as time spent by licking/biting of the injured paw. The second phase is generally defined as pain related events detected in the 15-60 min. time interval after formalin injection. It is known that NMDA receptors are involved in the second phase of response to formalin injection and this behavioural response is sensitive to blockade of NMDA receptors [Dickenson, A. and Besson J.-M. (Editors): Chapter 1, pp. 6-7: Animal models of Analgesia; and Chapter 8, pp. 180-183: Mechanism of Central Hypersensitivity: Excitatory Amino Acid Mechanisms and Their Control – In Pharmacology of Pain. Springer-Verlag (Berlin) 1997.] Therefore, we used the second phase of formalin test to characterise the efficacy of compounds in vivo. Inhibition of the second phase of response is considered to indicate an analgesic effect against chemically-induced persistent pain [Hunskaar, S., et al.: Formalin Test in Mice, a Useful Technique for Evaluating Mild Analgesics, Journal of Neuroscience Methods, 14 (1985) 69-76.]

Male albino Charles River NMRI mice (20-25 g) were used. Prior to the experiment any solid food was withdrawn for 16 hours but the animals had free access to 20 % glucose solution. The animals were allowed a 1 hour acclimatisation period spent in a glass cylinder (cc. 15 cm in

diameter), then moved to an identical cylinder with a mirror placed behind to facilitate observation. The test substances were suspended in 5 % tween-80 (10 ml per kg body weight). and administered orally by gavage 15 min before the formalin injection (20 µl of 1 % formalin in 0.9 % saline injected subcutaneously into the dorsal surface of the right hindpaw). The time spent by licking and biting of the injected paw was measured from 20 to 25 min. after the formalin injection. For the determination of ED_{50} value, various doses (at least five) of the test substances were given to groups of 5 mice and the results expressed as % inhibition time spent by licking relative to a vehicle control group observed on the same day. ED_{50} values (i.e. the dose yielding 50 % inhibition) were calculated by Boltzman's sigmoidal curve fitting.

Table 2

ED_{50} values of selected compounds

ID code of compounds	ED_{50} (mg/kg p.o.)
45-70001598	0.46
45-70002346	0.48
45-70002233	2.4
45-70002407	4.4
45-70001620	6.9
45-70002863	17
CI-1041	5.3 mg/kg
Co-101244	> 20 mg/kg*
EMD 95885	5.9 mg/kg
CP-101,606	>20 mg/kg*
Co-111103	>20 mg/kg*
Ro-256981	>20 mg/kg*

*: ED_{50} value was not determined if the inhibition was less than 50% at the dose of 20 mg/kg, p.o.

Disorders which may be beneficially treated with NMDA antagonists include traumatic injury of brain [Neurol. Res., 21, 330-338 (1999)] or spinal cord [Eur. J. Pharmacol., 175, 165-74 (1990)], human immunodeficiency virus (HIV) related neuronal injury [Annu. Rev. Pharmacol. Toxicol., 1998; 38159-77], amyotrophic lateral sclerosis [Neurol. Res., 21, 309-12 (1999)], tolerance and/or dependence to opioid treatment of pain [Brain. Res., 731, 171-181 (1996)], withdrawal syndromes of e.g. alcohol, opioids or cocaine [Drug and Alcohol Depend., 59, 1-15

(2000)], muscular spasm [Neurosci. Lett., 73, 143-148 (1987)], dementia of various origins [Expert Opin. Investig. Drugs, 9, 1397-406 (2000)]. An NMDA antagonist may also be useful to treat cerebral ischemia of any origin (e.g. stroke, heart surgery), chronic neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, pain (e.g. posttraumatic or postoperative) and chronic pain states, such as neuropathic pain or cancer related pain, epilepsy, anxiety, depression, migraine, psychosis, hypoglycemia, degenerative disorders of the retina (e.g. CMV retinitis), glaucoma, asthma, tinnitus, aminoglycoside antibiotic-induced 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, human immunodeficiency virus (HIV) related neuronal injury, amyotrophic lateral sclerosis, tolerance and/or dependence to opioid treatment of pain, withdrawal syndromes of e.g. alcohol, opioids or cocaine, ischemic CNS disorders, chronic neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, pain and chronic pain states, such as neuropathic pain or cancer related pain, epilepsy, anxiety, depression, migraine, psychosis, muscular spasm, dementia of various origin, hypoglycemia, degenerative disorders of the retina, glaucoma, asthma, tinnitus, aminoglycoside antibiotic-induced hearing loss.

The compounds of the invention as well as their pharmaceutically acceptable salts can be used as such or suitably in the form of pharmaceutical compositions. These compositions (drugs) can be in solid, liquid or semiliquid form and pharmaceutical adjuvant and auxiliary materials can be added, 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.

The dosage required to exert the therapeutical effect can vary within wide limits and will be fitted to the individual requirements in each of the particular cases, depending on the stage of the disease, the condition and the bodyweight of the patient to be treated, as well as the sensitivity of the patient against the active ingredient, route of administration and number of daily treatments. The actual dose of the active ingredient to be used can safely be determined by the attending physician skilled in the art in the knowledge of the patient to be treated.

The pharmaceutical compositions containing the active ingredient according to the present invention usually contain 0.01 to 100 mg of active ingredient in a single dosage unit. It is,

of course possible that the amount of the active ingredient in some compositions exceeds the upper or lower limits defined above.

The solid forms of the pharmaceutical compositions can be for example tablets, dragées, capsules, pills or lyophilized powder ampoules useful for the preparation of injections. Liquid compositions are the injectable and infusable compositions, fluid medicines, packing fluids and drops. Semiliquid compositions can be ointments, balsams, creams, shaking mixtures and suppositories.

For the sake of a simple administration it is suitable if the pharmaceutical compositions comprise dosage units containing the amount of the active ingredient to be administered once, or a few multiples or a half, third or fourth part thereof. Such dosage units are e.g. tablets, which can be powdered with grooves promoting the halving or quartering of the tablet in order to exactly administer the required amount of the active ingredient.

Tablets can be coated with an acid-soluble layer in order to assure the release of the active ingredient content after leaving the stomach. Such tablets are enteric-coated. A similar effect can be achieved also by encapsulating the active ingredient.

The pharmaceutical compositions for oral administration can contain e.g. lactose or starch as excipients, sodium carboxymethylcellulose, methylcellulose, polyvinyl pyrrolidine or starch paste as binders or granulating agents. Potato starch or microcrystalline cellulose is added as disintegration agents, but ultraamylopectin or formaldehyde casein can also be used. Talcum, colloidic silicic acid, stearin, calcium or magnesium stearate can be used as antiadhesive and lubricants.

The tablet can be manufactured for example by wet granulation, followed by pressing. The mixed active ingredients and excipients, as well as in given case part of the disintegrants are granulated with an aqueous, alcoholic or aqueous alcoholic solution of the binders in an appropriate equipment, then the granulate is dried. The other disintegrants, lubricants and antiadhesive agents are added to the dried granulate, and the mixture is pressed to a tablet. In given case the tablets are made with halving groove to ease the administration.

The tablets can be made directly from the mixture of the active ingredient and the proper auxiliaries by pressing. In given case, the tablets can be coated by using additives commonly used in the pharmaceutical practice, for example stabilizers, flavoring, coloring agents, such as sugar, cellulose derivatives (methyl- or ethylcellulose, sodium carboxymethylcellulose, etc), polyvinyl pyrrolidone, calcium phosphate, calcium carbonate, food coloring agents, food laces,

aroma agents, iron oxide pigments, etc. In the case of capsules the mixture of the active ingredient and the auxiliaries is filled into capsules.

Liquid oral compositions, for example suspensions, syrups, elixirs can be made by using water, glycols, oils, alcohols, coloring and flavoring agents.

For rectal administration the composition is formulated in suppositories or clysters. The suppository can contain beside the active ingredient a carrier, so called adeps pro suppository. Carriers can be vegetable oils, such as hydrogenated vegetable oils, triglycerides of C12-C18 fatty acids (preferably the carriers under the trade name Witepsol). The active ingredient is homogeneously mixed with the melted adeps pro suppository and the suppositories are moulded.

For parenteral administration the composition is formulated as injection solution. For manufacturing the injection solution the active ingredients are dissolved in distilled water and/or in different organic solvents, such as glycolethers, in given case in the presence of solubilizers, for example polioxyethylensorbitane-monolaurate, -monooleate, or monostearate (Tween 20, Tween 60, Tween 80). The injection solution can also contain different auxiliaries, such as conserving agents, for example ethylendiamine tetraacetate, as well as pH adjusting agents and buffers and in given case local anaesthetic, e.g. lidocain. The injection solution containing the active ingredient of the invention is filtered before it is filled into ampoules, and it is sterilized after filling.

If the active ingredient is hygroscopic, then it can be stabilized by liophylization.

The following examples illustrate the invention without the intention of limitation anyway.

Example 1

2-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-acetamide (45 70001598)

1a) [4-(4-Fluoro-benzyl)-piperidin-1-yl]-oxo-acetic acid ethyl ester

To a stirred solution of 2.3 g (10 mmol) of 4-(4-fluoro-benzyl)-piperidine hydrochloride [J. Med. Chem., **35**, 4903. (1992)] and 4.5 ml (32 mmol) of triethylamine in 80 ml of chloroform 2.5 ml (22 mmol) of ethyl oxalyl chloride in 20 ml of chloroform is added dropwise below 10 °C, and the reaction mixture is stirred at room temperature for 10 h. Then 50 ml of 8 % sodium hydrogen carbonate solution is added to the mixture, the organic layer is separated and the water phase is extracted three times with 25 ml of chloroform. The combined organic layers are dried over sodium sulfate, concentrated, the residue is treated with diisopropyl ether and the crystals are filtered to yield 2.1 g (72 %) of the title compound. Mp.: 72-74 °C (diisopropyl ether)

1b) [4-(4-Fluoro-benzyl)-piperidin-1-yl]-oxo-acetic acid

To a stirred solution of 1.91 g (6.5 mmol) of [(4-fluoro-benzyl)-piperidin-1-yl]-oxo-acetic-acid ethyl ester in 15 ml of ethanol is added a solution of 1.18 g (21.1 mmol) of potassium hydroxide in 3 ml of water. The reaction mixture is stirred at room temperature for 6 h then cooled and acidified with hydrochloric acid. The solid is collected, washed with water to yield 1.68. (97.4 %) g of the title compound. Mp.: 152-154 °C (ethanol-water)

1c) 2-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-acetamide

A mixture of 3.2 g (12 mmol) of [4-(4-fluoro-benzyl)-piperidin-1-yl]-oxo-acetic acid, 1.4 ml (10 mmol) of triethylamine, 1.5 g (10 mmol) of 5-amino-1,3-dihydro-indol-2-one [Tetrahedron, **24**, 1376. (1957)] 3.8 g (10 mmol) of HBTU [O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (Advanced Chem. Tech.)] and 100 ml of dimethylformamide is stirred at room temperature for 24 h. The reaction mixture is concentrated. Then 150 ml of 8 % sodium hydrogencarbonate solution and 150 ml of chloroform is added to the mixture. The organic layer is separated and the water phase is extracted three times with 25 ml of chloroform. The combined organic layers are dried over sodium sulfate, concentrated and the residue is purified by column chromatography using Kieselgel 60 as adsorbent (Merck) and chloroform : methanol =19 :1 as eluent to yield 2.67 g (68 %) of the title compound. Mp.: 195-197 °C (diethylether)

Example 2

2-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)-acetamide (45 70001623)

A mixture of 2.5 g (9.6 mmol) of [4-(4-fluoro-benzyl)-piperidin-1-yl]-oxo-acetic acid (Example 1b), 1.1 ml (8 mmol) of triethylamine, 1.2 g (8 mmol) of 5-amino-1,3-dihydro-benzimidazol-2-one [J. Amer. Chem. Soc., **80,** 1657. (1958)] 3.03 g (8 mmol) of HBTU and 80 ml of dimethylformamide is stirred at room temperature for 24 h. The reaction mixture is concentrated, then 100 ml of 8 % sodium hydrogencarbonate solution is added. The precipitated product is filtered off and recrystallized from methanol to yield 1.51 g (48 %) of the title compound. Mp.: > 260 °C (methanol)

Example 3

2-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide (45 70001620)

The title compound is prepared from [4-(4-fluoro-benzyl)-piperidin-1-yl]-oxo-acetic acid (Example 1b) and 6-amino-3H –benzoxazol-2-one [J. Chem. Soc., 321. (1938)] according to the method described in Example 1c. Mp.: 224-227 °C (diethylether)

Example 4

2-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-5-yl)-acetamide (45 70001759)

The title compound is prepared from 5-amino-3H-benzoxazol-2-one [J. Med. Chem., **10,** 408. (1967)] and [4-(4-fluoro-benzyl)-piperidin-1-yl]-oxo-acetic acid (Exmple 1b) according to the method described in Example 2. Mp.: 226-231 °C (water)

Example 5

2-(4-Benzyl-piperidin-1-yl]-N-(4-cyano-phenyl)-2-oxo-acetamide (45 70001798)

5a) (4-Benzyl-piperidine-1-yl)-oxo-acetic acid ethyl ester

The title compound is prepared from 4-benzyl-piperidine (Aldrich) and ethyl oxalyl chloride according to the method described in Example 1a. Mp.: oil

5b) (4-Benzyl-piperidin-1-yl)-oxo-acetic acid

The title compound is prepared from (4-benzyl-piperidin-1-yl)-oxo-acetic acid ethyl ester according to the method described in Example 1b. Mp.: 109-112 °C (ethanol-water)

5c) 2-(4-Benzyl-piperidin-1-yl)-N-(4-cyano-phenyl)-2-oxo-acetamide

The title compound is prepared from 4-amino-benzonitrile (Aldrich) and (4-benzyl-piperidin-1-yl)-oxo-acetic acid according to the method described in Example 2. Mp.: 166-169 °C (diethylether)

Example 6

2-(4-Benzyl-piperidin-1-yl)-2-oxo-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-acetamide (45 70001823)

The title compound is prepared from (4-benzyl-piperidin-1-yl)-oxo-acetic acid (Example 5b) and 5-amino-1,3-dihydro-indol-2-one according to the method described in Example 2. Mp.: 115-118 °C (water)

Example 7

2-(4-Benzyl-piperidin-1-yl)-2-oxo-N-(2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)-acetamide (45 70001824)

The title compound is prepared from (4-benzyl-piperidin-1-yl)-oxo-acetic acid (Example 5b) and 5-amino-1,3-dihydro-benzimidazol-2-one according to the method described in Example 2. Mp.: > 260 °C (water)

Example 8

2-(4-Benzyl-piperidin-1-yl)-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide (45 70001861)

The title compound is prepared from (4-benzyl-piperidin-1-yl)-oxo-acetic acid (Example 5b) and 6-amino-3H-benzoxazol-2-one according to the method described in Example 1c. Mp.:190-193 °C (diethylether)

Example 9

1-(4-Benzyl-piperidin-1-yl)-N-(1H-indazol-5-yl)-2-oxo-acetamide (45 70001814)

The title compound is prepared from 5-aminoindazol (Aldrich) and (4-benzyl-piperidin-1-yl)-oxo-acetic acid (Example 5b) according to the method described in Example 1c Mp.: 204-209 °C (diethylether)

Example 10

1-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-N-(1H-indazol-5-yl)-2-oxo-acetamide (45 70001816)

The title compound is prepared from 5-aminoindazol (Aldrich) and [4-(4-fluoro-benzyl)-piperidin-1-yl]-oxo-acetic acid (Example 1b) according to the method described in Example 2. Mp.: 198-200 °C (diethylether)

Example 11

2-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-2-oxo-N-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-7-yl)-acetamide (45 70001818)

The title compound is prepared from 7-amino-4H-benzo[1,4]oxazin-3-one [J. Med. Chem., **32**, 1627. (1989)] and [4-(4-fluoro-benzyl)-piperidin-1-yl]-oxo-acetic acid (Example 1b) according to the method described in Example 2. Mp.: 209-212 °C (diethylether)

Example 12

N-(1H-Benzimidazol-5-yl)-2-[4-(4-fluoro-benzyl)-piperidin-1-yl]-2-oxo-acetamide (45 70001820)

The title compound is prepared from (1H-benzimidazol-5yl) amine [Synth. Commun., **29**, 2435. (1999)] and [4-(4-fluoro-benzyl)-piperidin-1-yl]-oxo-acetic acid Example 1b) according to the method described in Example 1c. Mp.: 104-110 °C (diethylether)

Example 13

2-(4-Benzyl-piperidin-1-yl)-2-oxo-N-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-acetamide (45 70001844)

The title compound is prepared from 7-amino-4H-benzo[1,4]oxazin-3-one and (4-benzyl-piperidin-1-yl)-oxo-acetic acid (Example 5b) according to the method described in Example 2. Mp.: 123-126 °C (diethylether)

Example 14

2-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-N-(1H-indazol-6-yl)-2-oxo-acetamide (45 70001815)

The title compound is prepared from 6-aminoindazol (Aldrich) and [4-(4-fluoro-benzyl)-piperidin-1-yl]-oxo-acetic acid (Example 1b) according to the method described in Example 2. Mp.: 162-164 °C (diethylether)

Example 15

2-Oxo-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-2-(4-p-tolyloxy-piperidin-1-yl)-acetamide (45 70002274)

26a) Oxo-(4-p-tolyloxy-piperidin-1-yl)-acetic acid ethyl ester

The title compound is prepared from 4-p-tolyloxy-piperidine [J. Med. Chem., **21**, 309. (1978)] and ethyl oxalyl chloride according to the method described in Example 1a. Mp.: oil.

26b) Oxo-(4-p-tolyloxy-piperidin-1-yl)-acetic acid

The title compound is prepared from oxo-(4-p-tolyloxy-piperidin-1-yl)-acetic acid ethyl ester according to the method described in Example 1b. Mp.: 109-112 °C (ethanol-water).

26c) 2-Oxo-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-2-(4-p-tolyloxy-piperidin-1-yl)-acetamide

The title compound is prepared from oxo-(4-p-tolyloxy-piperidin-1-yl)-acetic acid and 5-amino-1,3-dihydro-indol-2-one according to the method described in Example 2. The filtered crystals are purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and toluene : methanol = 4 : 1 as eluent. Mp.: 176-178 °C (diethyl ether)

Example 16

2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-acetamide (45 70002365)

27a) [4-(4-Fluoro-phenoxy)-piperidin-1-yl]-oxo-acetic acid ethyl ester

The title compound is prepared from 4-(4-fluoro-phenoxy)-piperidine (US 3260723) and ethyl oxalyl chloride according to the method described in Example 1a. Mp.: oil

27b) [4-(4-Fluoro-phenoxy)-piperidin-1-yl]-oxo-acetic acid

The title compound is prepared from [4-(4-fluoro-phenoxy)-piperidin-1-yl]-oxo-acetic acid ethyl ester according to the method described in Example 1b. Mp.: 147-149 °C (ethanol-water)

27c) 2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-acetamide

The title compound is prepared from [4-(4-fluoro-phenoxy)-piperidin-1-yl]-oxo-acetic acid and 5-amino-1,3-dihydro-indol-2-one according to the method described in Example 2. The filtered crystals are purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and toluene : methanol = 4 : 1 as eluent. Mp.: 209-211 °C (diethyl ether)

Example 17

2-Oxo-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-2-(4-phenoxy-piperidin-1-yl)-acetamide (45 70002366)

28a) Oxo-(4-phenoxy-piperidin-1-yl)-acetic acid ethyl ester

The title compound is prepared from 4-phenoxy-piperidine (J. Med. Chem., **17**, 1000. (1974)] and ethyl oxalyl chloride according to the method described in Example 1a. Mp.: oil.

28b) Oxo-(4-phenoxy-piperidin-1-yl)-acetic acid

The title compound is prepared from oxo-(4-phenoxy-piperidin-1-yl)-acetic acid ethyl ester according to the method described in Example 1b. Mp.: 109-112 °C (ethanol-water).

28c) 2-Oxo-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-2-(4-phenoxy-piperidin-1-yl)-acetamide

The title compound is prepared from oxo-(4-phenoxy-piperidin-1-yl)-acetic acid and 5-amino-1,3-dihydro-indol-2-one according to the method described in Example 2. The filtered crystals are purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and toluene : methanol = 4 : 1 as eluent. Mp.: 78-81 °C (diethyl ether)

Example 19

2-[4-(4-Chloro-phenoxy)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-acetamide (45 70002367)

29a) 4-(4-Chloro-phenoxy)-piperidin-1-carboxylic acid tert-butyl ester

Under argon, to a stirred solution 10.0 g (49.7 mmol) of 4-hydroxy-piperidin-1-carboxylic acid tert-butyl ester [Bioorg. Med. Chem. Lett. **10,** 2815. (2000)] in 80 ml of dimethylformamide 3.0 g (60 % , 75 mmol) of sodium hydride is added . The reaction mixture is stirred for 1 h at 40 °C, then 5.3 ml (49.7 mmol) of 1-chloro-4-fluoro-benzene (Aldrich) in 20 ml dimethylformamide is added dropwise at 20°C. The reaction mixture is stirred for 4 h at 80 °C, cooled to 20 °C, 1 ml of ethanol is added dropwise, poured into 100 ml of water and extracted with ethyl acetate. The organic layer is dried over sodium sulfate and concentrated. The residue is purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and ethyl acetate as eluent to yield 11.07 g (75.5 %) of the title compound. Mp.: oil

29b) 4-(4-Chloro-phenoxy)-piperidine hydrochloride

To a solution of 150 ml of 2.5 M hydrochloric acid in ethyl acetate 11.07 g (37.5 mmol) of 4-(4-chloro-phenoxy)-piperidin-1-carboxylic acid tert-butyl ester is added. The reaction mixture is stirred for 3 h at 20 °C, then concentrated to 50 ml. The precipitated crystals are filtered off, washd with ethyl acetate to yield 7.0 g (75.2 %) of the title compound. Mp.: 194-196 °C.

29c) [4-(4-Chloro-phenoxy)-piperidin-1-yl]-oxo-acetic acid ethyl ester

The title compound is prepared from 4-(4-chloro-phenoxy)-piperidine and ethyl oxalyl chloride according to the method described in Example 1a. Mp.: oil.

29d) [4-(4-Chloro-phenoxy)-piperidin-1-yl]-oxo-acetic acid

The title compound is prepared from [4-(4-fluoro-phenoxy)-piperidin-1-yl]-oxo-acetic acid ethyl ester according to the method described in Example 1b. Mp.: 144-145 °C (ethanol-water)

29e) 2-[4-(4-Chloro-phenoxy)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-acetamide

The title compound is prepared from [4-(4-chloro-phenoxy)-piperidin-1-yl]-oxo-acetic acid and 5-amino-1,3-dihydro-indol-2-one according to the method described in Example 2. The filtered crystals are purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and toluene : methanol = 4 : 1 as eluent. Mp.: 198-200 °C (diethyl ether)

Example 19

2-[4-(4-Chloro-phenoxy)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)-acetamide (45 70002405)

The title compound is prepared from [4-(4-chloro-phenoxy)-piperidin-1-yl]-oxo-acetic acid (Example 29d) and 5-amino-1,3-dihydro-benzimidazol-2-one according to the method described in Example 2. The filtered crystals are purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and chloroform : methanol = 10 : 1 as eluent. Mp.: 286-288 °C (isopropanol)

Example 20

2-[4-(4-Chloro-phenoxy)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide (45 70002407)

The title compound is prepared from [4-(4-chloro-phenoxy)-piperidin-1-yl]-oxo-acetic acid (Example 29d) and 6-amino-3H-benzoxazol-2-one according to the method described in Example 2. The filtered crystals are purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and toluene : methanol = 4 : 1 as eluent. Mp.: 242-244 °C (isopropanol)

Example 21

2-(4-Benzyl-piperidin-1-yl)-2-oxo-N-(2-thioxo-2,3-dihydro-benzoxazol-6-yl)-acetamide (45 70002446)

To a stirred solution of 0.3 g (1.8 mmol) of 6-amino-3H-benzoxazole-2-thione [J. Org. Chem., **19**; 758. (1954)] and 0.6 ml (4.3 mmol) of triethylamine in 20 ml of chloroform 0.5 g (1.8 mmol) of (4-benzyl-piperidine-1-yl)-oxo-acetyl chloride (Example 38c) in 10 ml of chloroform is added dropwise at 0 °C. The reaction mixture is stirred at room temperature for 1 h, then washed with water and the organic layer is concentrated. The residue is purified by

column chromatography using Kieselgel 60 (Merck) as adsorbent and toluene : methanol = 4 : 1 as eluent to yield 0.46 g (61.9 %) of the title compound. Mp.: 203 °C (isopropanol)

Example 22

2-[4-(4-Chloro-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide (45 70002466)

33a) [4-(4-Chloro-benzyl)-piperidin-1-yl]-oxo-acetic acid ethyl ester

The title compound is prepared from 4-(4-chloro-benzyl)-piperidine (C.A. 77, 34266 w) and ethyl oxalyl chloride according to the method described in Example 1a. Mp.: oil

33b) [4-(4-Chloro-benzyl)-piperidin-1-yl]-oxo-acetic acid

The title compound is prepared from [4-(4-chloro-benzyl)-piperidin-1-yl]-oxo-acetic acid ethyl ester according to the method described in Example 1b. Mp.: 147-148 °C (ethanol-water).

33c) 2-[4-(4-Chloro-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide

The title compound is prepared from [4-(4-chloro-benzyl)-piperidin-1-yl]-oxo-acetic acid and 6-amino-3H–benzoxazol-2-one according to the method described in Example 2. The filtered crystals are purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and toluene : methanol = 4 : 1 as eluent. Mp.: 215 °C (isopropanol)

Example 23

2-[4-(4-Chloro-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)-acetamide (45 70002467)

The title compound is prepared from [4-(4-chloro-benzyl)-piperidin-1-yl]-oxo-acetic acid (Example 33b) and 5-amino-1,3-dihydro-benzimidazol-2-one according to the method described in Example 2. The filtered crystals are purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and toluene : methanol = 4 : 1 as eluent. Mp.: 299-300 °C (isopropanol)

Example 24

2-Oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-2-(4-p-tolyloxy-piperidin-1-yl)-acetamide (45 70002480)

The title compound is prepared from oxo-(4-p-tolyloxy-piperidin-1-yl)-acetic acid (Example 26b) and 6-amino-3H–benzoxazol-2-one according to the method described in Example 2. The filtered crystals are purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and toluene : methanol = 4 : 1 as eluent. Mp.: 203 °C (isopropanol)

Example 25

2-Oxo-N-(2-oxo-2,3-dihydro-1H-benzimidazol-6-yl)-2-(4-p-tolyloxy-piperidin-1-yl)-acetamide (45 70002481)

The title compound is prepared from oxo-(4-p-tolyloxy-piperidin-1-yl)-acetic acid (Example 26b) and 5-amino-1,3-dihydro-benzimidazol-2-one according to the method described in Example 2. The filtered crystals are purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and toluene : methanol = 4 : 1 as eluent. Mp.: 294 °C (isopropanol)

Example 26

2-[4-(4-Chloro-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-acetamide (45 70002486)

The title compound is prepared from [4-(4-chloro-benzyl)-piperidin-1-yl]-oxo-acetic acid (Example 33b) and 5-amino-1,3-dihydro-indol-2-one according to the method described in Example 2. The filtered crystals are purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and toluene : methanol = 4 : 1 as eluent. Mp.: 195 °C (isopropanol-diethyl ether)

Example 27

2-(4-Benzyl-piperidin-1-yl)-N-(2,3-dihydro-1H-indol-5-yl)-2-oxo-acetamide (45 70002497)

38a) 5-Nitro-2,3-dihydro-indol-1-carboxylic acid tert-butyl ester

A mixture of 10.0 g (61.0 mmol) of 5-nitro-2,3-dihydro-1H-indole (Aldrich), 100 ml of dichloromethane, 16.5 g (94.8 mmol) of di-tert-butyl dicarbonate, 13.2 ml (94.8 mmol) of trietylamine and 0.2 g (1.6 mmol) of 4-(dimethylamino)-pyridine is stirred at room temperature for 16 h. The reaction mixture is washed with water, dried over sodium sulfate and concentrated to yield 15.3 g (99.5 %) of the title compound. The crude product is used in the next step.

38b) 5-Amino-2,3-dihydro-indol-1-carboxylic acid tert-butyl ester

A mixture of 15.3 g (60.7 mmol) of 5-nitro-2,3-dihydro-indol-1-carboxylic acid tert-butyl ester, 200 ml of methanol, 200 ml of tetrahydrofuran and 1 g of 10 % Pd/C catalyst is hydrogenated. After completion of the reaction, the catalyst is filtered off, washed with tetrahydrofuran and the filtrate is concentrated. The residue is treated with a mixture of diisopropyl ether and hexane and the precipitated crystals are filtered off to yield 12.2 g (90.5 %) of the title compound. Mp.: 75-76 °C (isopropyl ether-hexane)

38c) (4-benzyl-piperidin-1-yl)-oxo-acetyl chloride

A mixture of 28.78 g (116.3 mmol) of (4-benzyl-piperidin-1-yl)-oxo-acetic acid (Example 5b) and 50 ml of thionyl chloride is refluxed for 2 h. The reaction mixture is concentrated to yield 30.5 g (98.6 %) of the title compound as a solid. The crude products is used in the next step.

38d) 5-[2-(4-Benzyl-piperidin-1-yl)-2-oxo-acetylamino]-2,3-dihydro-indol-1-carboxylic acid tert-butyl ester

To a stirred solution of 0.5 g (2.25 mmol) of 5-amino-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester and 0.4 ml (2.8 mmol) of triethylamine in 20 ml of chloroform 0.7 g (2.6 mmol) of (4-benzyl-piperidin-1-yl)-oxo-acetyl chloride in 10 ml of chloroform is added dropwise at 0 °C. The reaction mixture is stirred at room temperature for 1 h, then washed with water and the organic layer is concentrated. The residue is purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and toluene : methanol = 4 : 1 as eluent to yield 0.9 g (88.7 %) of the title compound as solid. The crude product is used in the next step.

38e) 2-(4-Benzyl-piperidin-1-yl)-N-(2,3-dihydro-1H-indol-5-yl)-2-oxo-acetamide

To a solution of 10 ml of 2.5 M hydrochloric acid in ethyl acetate 0.9 g (2.0 mmol) of 5-[2-(4-benzyl-piperidin-1-yl)-2-oxo-acetylamino]-2,3-dihydro-indol-1-carboxylic acid tert-butyl ester is added. The reaction mixture is stirred for 3 h at 20 °C, then concentrated. The product is transformed into base form with 2 M sodium carbonate solution, extracted with chloroform, the organic layer is concentrated and the residue is dried to yield 0.45 g (64.1 %) of the title compound. Mp.: 152 °C .

Example 28

N-(2-Amino-3H-benzimidazol-5-yl)-2-(4-benzyl-piperidin-1-yl)-2-oxo-acetamide trifluoroacetate (45 70002545)

39a) (5-Nitro-1H-benzimidazol-2-yl)-carbamic acid tert-butyl ester

(6-Nitro-1H-benzimidazol-2-yl)-carbamic acid tert-butyl ester

A mixture of 11.86 g (39.4 mmol) of 5-nitro-1(3)H-benzimidazol-2-ylamine nitrate (US 2324123), 150 ml of dichloromethane, 11.0 g (50.4 mmol) of di-tert-butyl dicarbonate and 14.0 ml (100.6 mmol) of trietylamine is stirred at room temperature for 16 h. The reaction mixture is washed with water, dried over sodium sulfate and concentrated. The residue is crystallized with isopropanol to yield 13.3 g (97.2 %) of a 1:1 mixture of the title compounds as solid. Mp.: 151-152 °C (isopropanol)

39b) (5-Amino-1H-benzimidazol-2-yl)-carbamic acid tert-butyl ester

(6-Amino-1H-benzimidazol-2-yl)-carbamic acid tert-butyl ester

A mixture of 13.3 g (47.8 mmol) of (5-nitro-1H-benzoimidazol-2-yl)-carbamic acid tert-butyl ester and (6-nitro-1H-benzimidazol-2-yl)-carbamic acid tert-butyl ester, 100 ml of methanol, 100 ml of tetrahydrofuran and 1 g of 10 % Pd/C catalyst is hydrogenated. After completion of the reaction, the catalyst is filtered off, washed with tetrahydrofuran and the filtrate is concentrated. The residue is purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and chloroform : methanol = 10 : 1 as eluent to yield 4.72 g (40.4 %) of (6-amino-1H-benzoimidazol-2-yl)-carbamic acid tert-butyl ester (Rf. 0.5), Mp.: 159 °C (diethyl ether) and 4.2 g (36.0 %) of (5-amino-1H-benzoimidazol-2-yl)-carbamic acid tert-butyl ester (Rf. 0.4) Mp.: 168 °C (diethyl ether)

39c) {5-[2-(4-Benzyl-piperidin-1-yl)-2-oxo-acetylamino]-1H-benzoimidazol-2-yl}-carbamic acid tert-butyl ester

To a stirred solution of 1.0 g (4.06 mmol) of (6-amino-1H-benzimidazol-2-yl)-carbamic acid tert-butyl ester and 0.8 ml (5.7 mmol) of triethylamine in 30 ml of chloroform 1.5 g (5.6 mmol) of (4-benzyl-piperidin-1-yl)-oxo-acetyl chloride (Example 38c) in 20 ml of chloroform is added dropwise at 0 °C. The reaction mixture is stirred at room temperature for 1 h, then washed with water and the organic layer is concentrated. The residue is crystallized with a mixture of chloroform-methanol = 10 : 1 to yield 1.3 g (67.1 %) of the title compound. Mp.: 192 °C (chloroform-methanol = 10 : 1).

39d) N-(2-Amino-3H-benzimidazol-5-yl)-2-(4-benzyl-piperidin-1-yl)-2-oxo-acetamide trifluoroacetate

To a solution of 5 ml of 5 % trifluoroacetic acid in dichloromethane 0.8 g (1.67 mmol) of {5-[2-(4-benzyl-piperidin-1-yl)-2-oxo-acetylamino]-1H-benzimidazol-2-yl}-carbamic acid tert-butyl ester is added. The reaction mixture is stirred for 48 h at 20 °C. The precipitated crystals are filtered off and washed with dichloromethane to yield 0.8 g (97.1 %) of the title compound. Mp.: 121 °C

Example 29

N-(2-Amino-benzthiazol-6-yl)-2-(4-benzyl-piperidin-1-yl)-2-oxo-acetamide (45 70002579)

The title compound is prepared from (4-benzyl-piperidin-1-yl)-oxo-acetic acid (Example 5b) and 2,6-diamino-benzthiazole [Arch. Pharm., **13,** 48. (1935)] according to the method described in Example 2. The filtered crystals are purified by column chromatography using

Kieselgel 60 (Merck) as adsorbent and toluene : methanol = 4 : 1 as eluent. Mp.: 203 °C (isopropanol)

Example 30

2-(4-Benzyl-piperidin-1-yl)-N-(2,2-dioxo-2,3-dihydro-1H-2λ^6-benzo[c]isothiazol-5-yl)-2-oxo-acetamide (45 70002724)

The title compound is prepared from (4-benzyl-piperidin-1-yl)-oxo-acetic acid (Example 5b) and 5-amino-1,3-dihydro-2,1-benzisothiazole-2,2-dioxide [J. Het. Chem., 23, 1645. (1986)] according to the method described in Example 2. The filtered crystals are purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and toluene : methanol = 4 : 1 as eluent. Mp.: 181-182 °C (isopropanol)

Example 31

2-[4-(4-tert-Butyl-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide (45 70002797)

42a) [4-(4-tert-Butyl-benzyl)-piperidin-1-yl]-oxo-acetic acid ethyl ester

The title compound is prepared from 4-(4-tert-butyl-benzyl)-piperidine [J. Org. Chem. **64,** 3763. (1999)] and ethyl oxalyl chloride according to the method described in Example 1a. Mp.: oil

42b) [4-(4-tert-Butyl-benzyl)-piperidin-1-yl]-oxo-acetic acid

The title compound is prepared from [4-(4-tert-butyl-benzyl)-piperidin-1-yl]-oxo-acetic acid ethyl ester according to the method described in Example 1b. Mp.: oil.

42c) 2-[4-(4-tert-Butyl-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide

The title compound is prepared from [4-(4-tert-butyl-benzyl)-piperidin-1-yl]-oxo-acetic acid and 6-amino-3H–benzoxazol-2-one according to the method described in Example 2. The filtered crystals are purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and toluene : methanol = 4 : 1 as eluent. Mp.: 168 °C (diethyl ether-hexane-diisopropyl ether).

Example 32

2-[4-(4-Cyano-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide (45 70002844)

43a) 4-(1-Benzyl-piperidin-4-ylidenemethyl)-benzonitrile

Under argon, to a stirred solution of 5.0 g (26.4 mmol) of N-benzyl-4-piperidone (Aldrich) and 7.0 g (27.6 mmol) of (4-cyano-benzyl)-phosphoric acid diethyl ester [J. Chem. Soc.

Perkin Trans 2., 3, 395. (2001)]) in 50 ml of dimethylformamide 1.5 g (60 % , 37.5 mmol) of sodium hydride is added at 0 °C. The reaction mixture is stirred for 4 h at 20 °C , 1 ml of ethanol is added dropwise, poured into 100 ml of water and extracted with diethyl ether. The organic layer is dried over sodium sulfate and concentrated. The crude product is used in the next step. Mp.: oil.

43b) 4-(1-Benzyl-piperidin-4-ylmethyl)-benzonitrile

A mixture of 8.25 g (28.6 mmol) of 4-(1-benzyl-piperidin-4-ylidenemethyl)-benzonitrile, 200 ml of ethanol and 0.5 g of 10 % Pd/C catalyst is hydrogenated . After completion of the reaction, the catalyst is filtered off, washed with tetrahydrofuran and the filtrate is concentrated. The residue is purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and toluene : methanol = 4 : 1 as eluent. Mp.: 95-96 °C (diisopropyl ether).

43c) 4-Piperidin-4-ylmethyl-benzonitrile hydrochloride

To a stirred solution of 0.5 g (1.72 mmol) of 4-(1-benzyl-piperidin-4-ylmethyl)-benzonitrile in 3 ml of dichloroethan 0.2 ml (1.85 mmol) of 1-chloroethyl-chloroformate is added dropwise at 0 °C. The reaction mixture is stirred at 0 °C for 1h and refluxed for 8 h, then concentrated and the residue is refluxed in 10 ml of methanol. The reaction mixture is concentrated and the residue is crystallized with isopropanol to yield 0.384 g (94.4 %) of the title compound. Mp.: 194 °C (isopropanol).

43d) N-(2-Oxo-2,3-dihydro-benzoxazol-6-yl)-oxalamic acid ethyl ester

The title compound is prepared from 6-amino-3H–benzoxazol-2-one and ethyl oxalyl chloride according to the method described in Example 1a. Mp.: 180-186 °C.

43e) N-(2-Oxo-2,3-dihydro-benzoxazol-6-yl)-oxalamic acid

The title compound is prepared from N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-oxalamic acid ethyl ester according to the method described in Example 1b. Mp.: 254 °C (ethanol-water)

43f) 2-[4-(4-Cyano-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide

To a mixture of 0.3g (1.5 mmol) of N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-oxalamic acid, 0.165 ml (1.5 mmol) of N-methyl-morpholine in 8 ml of dimethylformamid 0.2 ml (1.5 mmol) of isobutyl-chloroformate is added dropwise at 0°C and the mixture is stirred at 0°C for 1 h. Then 0.333 g (1.4 mmol) of 4-piperidin-4-ylmethyl-benzonitrile hydrochloride and 0.165 ml (1.5 mmol) of N-methyl-morpholine are added and the reaction mixture is stirred at 0°C for 1 h, at room temperature for 16 h. The reaction mixture is concentrated and the residue is purified by

column chromatography using Kieselgel 60 (Merck) as adsorbent and toluene : methanol = 4 : 1 as eluent to yield 0.045 g (8.0 %) of the title compound. Rf.: 0.4. Mp.: 259-260 °C (isopropanol).

Example 33

2-Oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-2-[4-(4-trifluoromethyl-benzyl)-piperidin-1-yl]-acetamide (45 70002930)

The title compound is prepared from 4-(4-trifluoromethyl-benzyl)-piperidine [J. Org. Chem., 64, 3763. (1999)] and N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-oxalamic acid (Example 43e) according to the method described in Example 43f. The residue is purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and toluene : methanol = 4 : 1 as eluent. Mp.: 217 °C (isopropanol)

Example 34

2-[4-(2,4-Difluoro-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide (45 70002931)

45a) 4-(2,4-Difluoro-benzylidene)-piperidin-1-carboxylic acid tert-butyl ester

The title compound is prepared from N-(tert-butoxycarbonyl)-4-piperidone and (2,4-difluoro-benzyl)-phosphoric acid diethyl ester [Eur. J. Med. Chim. Ther., 27, 845. (1992)] according to the method described in Example 43a. The residue is purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and hexane : ethyl acetate = 4 : 1 as eluent. Mp.: oil

45b) 4-(2,4-Difluoro-benzyl)-piperidin-1-carboxylic acid tert-butyl ester

The title compound is prepared from 4-(2,4-difluoro-benzylidene)-piperidin-1-carboxylic acid tert-butyl ester according to the method described in Example 43a. The crude product is used in the next step. Mp.: oil

45c) 4-(2,4-Difluoro-benzyl)-piperidine

The title compound is prepared from 4-(2,4-difluoro-benzyl)-piperidin-1-carboxylic acid tert-butyl ester according to the method described in Example 29b. Mp.: 191°C (ethyl acetate-diethyl ether)

45d) 2-[4-(2,4-Difluoro-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide

The title compound is prepared from 4-(2,4-difluoro-benzyl)-piperidine and N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-oxalamic acid (Example 43e) according to the method described in

Example 43f. The residue is purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and toluene : methanol = 4 : 1 as eluent. Mp.: 231 °C (isopropanol)

Example 35

N-(2,2-Dioxo-2,3-dihydro-1H-2λ^6-benzo[c]isothiazol-5-yl)-2-[4-(4-fluoro-benzyl)-piperidin-1-yl)-2-oxo-acetamide (45 70002966)

The title compound is prepared from [4-(4-fluoro-benzyl) piperidin-1-yl]-oxo-acetic acid (Example 1a) and 5-amino-1,3-dihydro-2,1-benzisothiazole-2,2-dioxide according to the method described in Example 2. The filtered crystals are purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and toluene : methanol = 4 : 1 as eluent. Mp.: 183-184 °C (isopropanol)

Example 36

2-[4-(3,4-Difluoro-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide (45 70002967)

The title compound is prepared from 4-(3,4-difluoro-benzyl)-piperidine [J. Org. Chem., **64,** 3763. (1999)] and N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-oxalamic acid (Example 43e) according to the method described in Example 43f. The residue is purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and toluene : methanol = 4 : 1 as eluent. Mp.: 233 °C (isopropanol)

Example 37

2-(4-Benzyl-piperidin-1-yl)-2-oxo-N-(2-trifluoromethyl-1H-benzoimidazol-5-yl)-acetamide (45 70002968)

The title compound is prepared from (4-benzyl-piperidin-1-yl)-oxo-acetic acid (Example 5b) and 2-trifluoromethyl-1(3)H-benzimidazol-5-ylamine (NL 6501323, CA 66; 28771) according to the method described in Example 2. The filtered crystals are purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and toluene : methanol = 4 : 1 as eluent. Mp.: 142 °C (isopropanol).

Example 38

2-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-2-oxo-N-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-acetamide (45 70001819)

The title compound is prepared from 6-amino-4H-benzo[1,4]oxazin-3-one [Indian J. Chem. Sect. B, **24,** 1263. (1985)] and [4-(4-fluoro-benzyl)-piperidin-1-yl]-oxo-acetic acid (Example 1b) according to the method described in Example 2. Mp.: 197-200 °C (diethylether)

Example 39

2-(4-Benzyl-piperidin-1-yl)-2-oxo-N-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-acetamide (45 70001845)

The title compound is prepared from 6-amino-4H-benzo[1,4]oxazin-3-one and (4-benzyl-piperidin-1-yl)-oxo-acetic acid (Example 5b) according to the method described in Example 1c. Mp.: 186-187 °C (diethylether)

Example 40

2-(4-Benzyl-piperidin-1-yl)-N-(1H-benzimidazol-5-yl) 2-oxo-acetamide (45 70001846)

The title compound is prepared from 5-amino-benzimidazole and (4-benzyl-piperidin-1-yl)-oxo-acetic acid (Example 5b) according to the method described in Example 1c. Mp.: 85-87 °C (diethylether)

Example 41

2-(4-Benzyl-piperidin-1-yl)-N-(1H-indazol-6-yl)-2-oxo-acetamide (45 70001878)

The title compound is prepared from 6-aminoindazol (Aldrich) and (4-benzyl-piperidin-1-yl)-oxo-acetic acid (Example 5b) according to the method described in Example 1c. Mp.: 160-164 °C (diethylether).

Example 42

2-(4-Benzyloxy-piperidin-1-yl)-2-oxo-N-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-acetamide (45 70002186)

53a) N-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-oxalamic acid ethyl ester

The title compound is prepared from 7-amino-4H-benzo[1,4]oxazine-3-one [J. Med. Chem., **32,** 1627. (1989)] and ethyl chlorooxoacetate (Aldrich) according to the method described in Example 1a. Mp.: 239-240 °C (water)

53b) N-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-oxalamic acid

The title compound is prepared from N-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-oxalamic acid ethyl ester and potassium hydroxide according to the method described in Example 1b. Mp.: 232.5-235.5 °C (water)

53c) 2-(4-Benzyloxy-piperidin-1-yl)-2-oxo-N-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-acetamide

The title compound is prepared from N-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-oxalamic acid and 4-benzyloxy-piperidine [Tetrahedron Lett., **36,** 3465. (1995)] according to the method described in Example 1c. Mp.: 143-146 °C (diethylether)

Example 43

2-Oxo-N-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-2-(4-phenoxy-piperidin-1-yl)-acetamide (45 70002188)

The title compound is prepared from N-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-oxalamic acid (Example 53b) and 4-phenoxypiperidine according to the method described in Example 2. Mp.: 196-199 °C (diethylether)

Example 44

2-Oxo-N-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-2-(4-phenoxy-methyl-piperidin-1-yl)-acetamide (45 70002244)

The title compound is prepared from N-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-oxalamic acid (Example 53b) and 4-phenoxy-methyl-piperidine [DE 254 999 (1977)] according to the method described in Example 1c. Mp.: 215-217 °C (diethylether)

Example 45

2-Oxo-N-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-2-(4-phenethyl-piperidin-1-yl)-acetamide (45 70002250)

The title compound is prepared from N-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-oxalamic acid (Example 53b) and 4-phenethyl-piperidine [J. Amer. Chem. Soc., **72,** 4953. (1950)] according to the method described in Example 1c. Mp.: 128-132 °C (diethylether)

Example 46

2-[4-(Hydroxy-phenyl-methyl)-piperidin-1-yl]-2-oxo-N-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-acetamide (45 70002251)

The title compound is prepared from N-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-oxalamic acid (Example 53b) and phenyl-piperidine-4-yl-methanol [J. Amer. Chem. Soc.,**52,** 4006. (1930)] according to the method described in Example 1c. Mp.: 195-197 °C (diethylether)

Example 47

2-Oxo-N-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-2-(4-p-tolyloxy-piperidin-1-yl)-acetamide (45 70002333)

The title compound is prepared from N-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-oxalamic acid (Example 53b) and 4-p-tolyloxy-piperidine according to the method described in Example 1c. Mp.: 226-228 °C (diethylether)

Example 48

2-[4-(4-Methylbenzyl)-piperidin-1-yl]-2-oxo-N-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-acetamide (45 70002339)

The title compound is prepared from N-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-oxalamic acid (Example 53b) and 4-(4-methylbenzyl)-piperidine [J Org. Chem., 64,3763. (1999)] according to the method described in Example 1c. Mp.: 228-231 °C (diethylether)

Example 49

2-(4-Benzyl-piperidin-1-yl)-N-(2-mercapto-3H-benzimidazol-5-yl)-2-oxo-acetamide (45 70002567)

60a) N-(2-Mercapto-3H-benzimidazol-5-yl)-oxalamic acid ethyl ester

The title compound is prepared from 6-amino-1H-benzimidazol-2-thiol [J. Chem. Soc., 1515 (1950)] and ethyl chlorooxoacetate (Aldrich) according to the method described in Example 1a Mp.: 225-226 °C (water)

60b) N-(2-Mercapto-3H-benzimidazol-5-yl)-oxalamic acid

The title compound is prepared from N-(2-mercapto-3H-benzimidazole-5-yl)-oxalamic acid ethyl ester and potassium hydroxide according to the method described in Example 1b Mp.: 276-280 °C (water)

60c) 2-(4-Benzyl-piperidin-1-yl)-N-(2-mercapto-3H-benzimidazol-5-yl)-2-oxo-acetamide

The title compound is prepared from N-(2-mercapto-3H-benzimidazol-5-yl)-oxalamic acid and 4-benzyl-piperidine according to the method described in Example 1c. Mp.: 277-281 °C (diethylether)

Example 50

2-(4-Benzyl-piperidin-1-yl)-2-oxo-N-(2-oxo-2,3-dihydro-benzothiazol-6-yl)-acetamide (45 70002568)

61a) N-(2-Oxo-2,3-dihydro-benzothiazol-6-yl)-oxalamic acid ethyl ester

The title compound is prepared from 6-amino-3H-benzothiazol-2-one [Liebigs Ann. Chem., 277, 244 (1893)] and ethyl chlorooxoacetate (Aldrich) according to the method described in Example 1a Mp.: 226-231 °C (water)

61b) N-(2-Oxo-2,3-dihydro-benzothiazol-6-yl)-oxalamic acid

The title compound is prepared from N-(2-oxo-2,3-dihydro-benzothiazol-6-yl)-oxalamic acid ethyl ester and potassium hydroxide according to the method described in Example 1b Mp.: 275-278 °C (water)

61c) 2-(4-Benzyl-piperidin-1-yl)-2-oxo-N-(2-oxo-2,3-dihydro-benzothiazol-6-yl)-acetamide

The title compound is prepared from N-(2-oxo-2,3-dihydro-benzothiazole-6-yl)-oxalamic acid and 4-benzylpiperidine according to the method described in Example 1c. Mp.: 201-203 °C (diethylether)

Example 51

2-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-N-(2-mercapto-3H-benzimidazol-5-yl)-2-oxo-acetamide (45 70002569)

The title compound is prepared from N-(2-mercapto-3H-benzimidazol-5-yl)-oxalamic acid (Example 60b) and 4-(4-fluoro-benzyl)-piperidine according to the method described in Example 1c. Mp.: 286-288 °C (diethylether)

Example 52

2-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzothiazol-6-yl)-acetamide (45 70002615)

The title compound is prepared from N-(2-oxo-2,3-dihydro-benzothiazol-6-yl)-oxalamic acid (Example 61b) and 4-(4-fluoro-benzyl)-piperidine according to the method described in Example 1c. Mp.: 223.5-225.5 °C (diethylether)

Example 53

2-Oxo-N-(2-oxo-2,3-dihydro-benzothiazol-6-yl)-2-(4-p-tolyloxy-piperidin-1-yl)-acetamide (45 70002706)

The title compound is prepared from N-(2-oxo-2,3-dihydro-benzothiazol-6-yl)-oxalamic acid (Example 61b) and 4-p-tolyloxy-piperidine according to the method described in Example 1c. Mp.: 215-217 °C (diethylether)

Example 54

2-[4-(4-Methyl-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzothiazol-6-yl)-acetamide (45 80002247)

The title compound is prepared from N-(2-oxo-2,3-dihydro-benzothiazol-6-yl)-oxalamic acid (Example 61b) and 4-(4-methyl-benzyl)-piperidine according to the method described in Example 1c. Mp.: 221-222 °C (diethylether)

Example 55

2-[4-(4-Chloro-phenoxy)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzothiazol-6-yl)-acetamide (45 80002398)

The title compound is prepared from N-(2-oxo-2,3-dihydro-benzothiazol-6-yl)-oxalamic acid (Example 61b) and 4-(4-chloro-benzyl)-piperidine according to the method described in Example 1c. Mp.: 245-247 °C (diethylether)

Example 56

N-(2-Mercapto-3H-benzimidazol-5-yl)-2-(4-p-tolyloxy-piperidin-1-yl)-2-oxo-acetamide (45 70002739)

The title compound is prepared from N-(2-mercapto-3H-benzimidazol-5-yl)-oxalamic acid (Example 60b) and 4-p-tolyloxy-piperidine according to the method described in Example 1c. Mp.: 311-314 °C (diethylether)

Example 57

2-(4-Benzyl-piperidin-1-yl)-2-oxo-N-(3-thioxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-acetamide (45 70002614)

68a) 7-amino-4H-benzo[1,4]oxazin-3-thione

A stirred mixture of 1.0 g of 7-nitro-4H-benzo[1,4]oxazin-3-thione [Indian J. Chem. Sect. B, 12, 1279. (1984)] and 4.0 g of sodium dithionite in 30 ml of ethanol and 30 ml of water is refluxed for 2 h. Then the reaction mixture is concentrated and the residue is submitted to column chromatography using Kieselgel 60 as adsorbent (Merck) and chloroform : methanol = 9 :1 as eluent to yield 0.33 g (38 %) of the title compound. Mp.: 205-211 °C (diethylether)

68b) 2-(4-Benzyl-piperidin-1-yl)-2-oxo-N-(3-thioxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-acetamide

The title compound is prepared from 7-amino-4H-benzo[1,4]oxazin-3-thione and (4-benzyl-piperidin-1-yl)-oxo-acetic acid (Example 5b) according to the method described in Example 1c. Mp.: 193-196 °C (diethylether)

Example 58

2-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-N-(indan-5-yl)-2-oxo-acetamide (45 70002198)

The title compound is prepared from [4-(4-fluoro-benzyl)-piperidin-1-yl]-oxo-acetic acid (Example 1b) and 5-aminoindan (Aldrich) according to the method described in Example 1c. Mp.: 150-152 °C (diethylether)

Example 59

2-(4-Benzyl-piperidin-1-yl)-N-(indan-5-yl)-2-oxo-acetamide (45 70002224)

The title compound is prepared from (4-benzyl-piperidin-1-yl)-oxo-acetic acid (Example 5b) and 5-aminoindan (Aldrich) according to the method described in Example 1c.

Mp.: 106-109 °C (diethylether)

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Example 60

2-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-N-(1H-indol-5-yl)-2-oxo-acetamide (45 70002239)

The title compound is prepared from [4-(4-fluoro-benzyl)-piperidin-1-yl]-oxo-acetic acid (Example 1b) and 5-amino-indole (Aldrich) according to the method described in Example 1c. Mp.: 80-82 °C (ethyl acetate)

Example 61

N-(4-Bromo-phenyl)-2-[4-(4-fluoro-benzyl)-piperidin-1-yl]-2-oxo-acetamide (45 70002307)

A mixture of 0.64 g (2.4 mmol) of [4-(4-fluoro-benzyl)piperidin-1-yl]-oxo-acetic acid, 0.34 ml (2.4 mmol) of triethylamine, 0.35 g (2 mmol) of 4-bromo-aniline (Aldrich), 0.91 g (2.4 mmol) of HBTU and 10 ml of dimethylformamide is stirred at room temperature for 24 h. The reaction mixture is concentrated. Then 30 ml of 8 % sodium hydrogencarbonate solution and 30 ml of chloroform is added to the mixture. The organic layer is separated and the water phase is extracted three times with 20 ml of chloroform. The combined organic layers are dried over sodium sulfate, concentrated. The residue is treated with diethylether and the crystals are filtered off to yield 0.36 g (43 %) of the title compound. Mp.: 156-158 °C (diethylether)

Example 62

2-[4-[4-Methyl-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-acetamide (45 70002346)

101a) N-(2-Oxo-2,3-dihydro-1H-indol-5-yl)-oxalamic acid ethyl ester

The title compound is prepared from 1-amino-1,3-dihydro-indol-2-one and ethyl oxalyl chloride according to the method described in Example 1a. Mp.: 235-237 °C (diethylether)

101b) N-(2-Oxo-2,3-dihydro-1H-indol-5-yl)-oxalamic acid

The title compound is prepared from N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-oxalamic acid ethyl ester and potassium hydroxide according to the method described in Example 1b. Mp.: 256 °C (water)

101c) 2-[4-[4-Methyl-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-acetamide

The title compound is prepared from N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-oxalamic acid and 4-(4-methyl-benzyl)-piperidine according to the method described in Example 1c. Mp.: 196-199 °C (diethylether)

Example 63

2-(4-Benzyl-piperidin-1-yl)-N-(1H-indol-5-yl)-2-oxo-acetamide (45 70002347)

The title compound is prepared from 5-aminoindole (Aldrich) and (4-benzyl-piperidin-1-yl)-oxo-acetic acid (Example 5b) according to the method described in Example 1c. Mp.: 68-72 °C (hexane)

Example 64

2-[(4-Hydroxy-phenyl-methyl)-piperidin-1-yl]-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-2-oxo-acetamide 45 70002348

The title compound is prepared from N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-oxalamic acid (Example 101b) and phenyl-[4]piperidyl-methanol according to the method described in Example 1c. Mp.: 88-100 °C (dec.) (diethylether)

Example 65

2-[4-[2-Methyl-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-acetamide (45 70002350)

The title compound is prepared from N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-oxalamic acid (Example 101b) and 4-(2-methyl-benzyl)-piperidine [J. Org. Chem., 64, 3763. (1999)] according to the method described in Example 1c. Mp.: 211-213 °C (diethylether)

Example 66

2-Oxo-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-2-(4-phenoxymethyl-piperidin-1-yl)-acetamide (45 70002351)

The title compound is prepared from N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-oxalamic acid (Example 101b) and 4-phenoxy-methyl-piperidine according to the method described in Example 1c. Mp.: 200-202 °C (diethylether)

Example 67

2-[4-[4-Methoxy-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-acetamide (45 70002391)

The title compound is prepared from N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-oxalamic acid (Example 101b) and 4-(4-methoxy-benzyl)-piperidine [US 3632767 (1972)] according to the method described in Example 1c. Mp.: 215-217 °C (diethylether)

Example 68

2-[4-[3-Fluoro-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-acetamide (45 70002439)

The title compound is prepared from N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-oxalamic acid (Example 101b) and 4-(3-fluoro-benzyl)-piperidine [J. Org. Chem. 64, 3763. (1999)] according to the method described in Example 1c. Mp.: 182-184 °C (diethylether)

Example 69

2-Oxo-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-2-(4-phenethyl-piperidin-1-yl)-acetamide (45 70002440)

The title compound is prepared from N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-oxalamic acid (Example 101b) and 4-phenethyl-piperidine according to the method described in Example 1c. Mp.: 236-240 °C (diethylether)

Example 70

2-[4-(4-Methyl-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl]-acetamide (45 70002764)

119a) [4-(4-Methyl-benzyl)-piperidin-1-yl]-oxo-acetic acid ethyl ester

The title compound is prepared from 4-(4-methyl-benzyl)-piperidin and ethyl oxalyl chloride according to the method described in Example 1a. Mp.: oil

119b) [4-(4-Methyl-benzyl)-piperidin-1-yl]-oxo-acetic acid

The title compound is prepared from [4-(4-methyl-benzyl-piperidin-1-yl)-oxo-acetic acid ethyl ester according to the method described in Example 1b. Mp.: 133-135 °C (ethanol-water)

119c) 2-[4-(4-methyl-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl]-acetamide

The title compound is prepared from 5-amino-1,3-dihydro-indol-2-one and [4-(4-methyl-benzyl)-piperidin-1-yl)-oxo-acetic acid according to the method described in Example 1c. Mp.: 216-220 °C (diethylether)

Example 71

2-[4-[4-Methoxy-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide (45 70002777)

The title compound is prepared from N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-oxalamic acid (Example 43e) and 4-(4-methoxy-benzyl)-piperidine according to the method described in Example 1c. Mp.: 193-197 °C (diisopropylether)

Example 72

2-[4-[3-Methoxy-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide (45 70002838)

The title compound is prepared from N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-oxalamic acid (Example 43e) and 4-(3-methoxy-benzyl)-piperidine [US 3632767 (1972)] according to the method described in Example 2. Mp.: 110-115 °C (diisopropylether)

Example 73

2-[4-[3-Methyl-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide (45 70002839)

The title compound is prepared from N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-oxalamic acid (Example 43e) and 4-(3-methyl-benzyl)-piperidine according to the method described in Example 2. Mp.: 204-208 °C (diisopropylether)

The title compound is prepared from 5-amino-1H-indole-2,3-dion [Helv. Chim-Acta **19**, 1327. (1936)] and (4-benzyl-piperidin-1-yl)-oxo-acetic-acid (Example 5b) according to the method described in Example 1c. Mp.: 234-236 °C (diethylether)

Example 79

2-[4-(4-Methyl-benzyl)-piperidin-1-yl)-2-oxo-N-(2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)-acetamide (45 80002201

The title compound is prepared from [4-(4-methyl-benzyl)-piperidin-1-yl]-oxo-acetic acid (Example 119b) and 5-amino-1,3-dihydro-benzimidazole-2-one according to the method described in Example 1c. Mp.: > 280 °C (diethylether)

Example 80

2-[4-(4-Methyl-benzyl)-piperidin-1-yl)-2-oxo-N-(2-oxo-1,2,3,4-tetrahidro-quinolin-6-yl-acetamide (45 80002221)

The title compound is prepared from [4-(4-methyl-benzyl)-piperidin-1-yl]-oxo-acetic acid (Example 119b) and 6-amino-3,4-dihydro-1H-quinoline-2-one [J.Chem. Soc., 183. (1969)] according to the method described in Example 2. Mp.: 209-213 °C (water)

Example 81

2-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-N-(2-oxo-2,3-dihydro-1H-benzoxazol-6-yl)-acetamide (45 70001655)

142a) 2-Chloro-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide

To a stirred solution of 1.5 g (10 mmol) of 6-amino-3H-bezonzoxazol-2-one and 3.4 ml (24 mmol) of triethylamine in 90 ml of chloroform 2 ml (24 mmol) of chloroacetyl chloride in 20 ml of chloroform is added dropwise below 10 °C, and the reaction mixture is stirred at room temperature for 10 h. The reaction mixture is concentrated and 100 ml of 8 % sodium hydrogencarbonate solution is added to the residue. The precipitated product is filtered off, and washed with water to yield 1.76 g (78 %) of the title compound. Mp.: 228-231 °C (water)

142b) 2-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-N-(2-oxo-2,3-dihydro-1H-benzoxazol-6-yl)-acetamide

A mixture of 0.91 g (4 mmol) of 2-chloro-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide, 0.7 g (4 mmol) of potassium iodide, 1.2 ml (8 mmol) of triethylamine, 0.7 g (3 mmol) of 4-(4-fluoro-benzyl)-piperidine hydrochloride and 50 ml of acetonitrile is refluxed for 20 h. The reaction mixture is concentrated and 30 ml of water and 30 ml of chloroform are added to the residue. The organic layer is separated and the water phase is extracted three times with 10 ml of chloroform. The combined organic layers are dried over sodium sulfate, concentrated and the residue is purified by column chromatography using Kieselgel 60 adsorbent (Merck) and chloroform :methanol = 97:3 as eluent to yield 0.3 g (26 %) of the title compound. Mp.: 232-234 °C (diethylether)

Example 82

2-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-N-(2-oxo-2,3-dihydro-1H-benzoxazol-6-yl)-acetamide hydrochloride (45 70002909)

To a stirred suspension of 1,5 g (3.9 mmol) of 2-[4-(4-fluoro-benzyl)-piperidin-1-yl]-N-(2-oxo-2,3-dihydro-1H-benzoxazol-6-yl)-acetamide (Example 142 b) in 40 ml of diethylether is added 4 ml of 2.5 N hydrochloric acid in ethyl acetate. The mixture is stirred for 1h at room temperature, the crystals are filtered off and washed with diethylether to yield 1.64 g (100 %) of the title compound. Mp.: 210-216 °C (dec.) (diethylether)

Example 83

5-{2-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-2-oxo-ethylamino}-1,3-dihydro-benzoimidazol-2-one (45 70001863)

197a) 2-Chloro-1-[4-(4-fluoro-benzyl)-piperidin-1-yl]-ethanone

The title compound is prepared from 4-(4-fluoro-benzyl)-piperidine and chloroacetyl chloride according to the method described in Example 142a. Mp.: 85-87 °C (water)

197b) 5-{2-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-2-oxo-ethylamino}-1,3-dihydro-benzimidazol-2-one

The title compound is prepared from 2-chloro-1-[4-(4-fluoro-benzyl)-piperidine-1-yl]-ethanone and 5-amino-1,3-dihydro-benzimidazol-2-one according to the method described in Example 142b. Mp.: 249-251 °C (diethylether)

Example 84

6-{2-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-2-oxo-ethylamino}-3H-benzoxazol-2-one (45 70001944)

The title compound is prepared from 2-chloro-1-[4-(4-fluoro-benzyl)-piperidin-1-yl]-ethanone (Example 197a) and 6-amino-3H-benzoxazol-2-one according to the method described in Example 142b. Mp.: 202-205 °C (diethylether)

Example 85

1-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-2-(1H-indazol-5-yl-amino)-ethanone (45 70001843)

The title compound is prepared from 5-aminoindazol (Aldrich) and 2-chloro-1-[4-(4-fluoro-benzyl)-piperidin-1-yl]-ethanone (Example 197a) according to the method described in Example 142b. Mp.: 113-114 °C (diethylether)

Example 86

1-(4-Benzyl-piperidin-1-yl)-2-(1H-indazol-5-yl-amino)-ethanone (45 70001949)

200a) 2-Chloro-1-(4-benzyl-piperidin-1-yl)-ethanone

The title compound is prepared from 4-benzyl-piperidine and chloroacetyl chloride according to the method described in Example 142a. Mp.: 42-47 °C

200b) 1-(4-benzyl-piperidin-1-yl)-2-(1H-indazol-5-yl-amino)-ethanone

The title compound is prepared from 5-aminoindazol and 2-chloro-1-(4-benzyl-piperidin-1-yl)-ethanone according to the method described in Example 142b. Mp.: 153-155 °C (diethylether)

Example 87

2-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-7-yl-amino)-ethanone (45 70002015)

The title compound is prepared from 7-amino-4H-benzo[1,4]oxazine-3-one and 2-chloro-1-[4-(4-fluoro-benzyl)-piperidin-1-yl]-ethanone (Example 197a) according to the method described in Example 142b. Mp.: 156-161 °C (diethylether).

Example 88

2-(4-Benzyl-piperidin-1-yl)-2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-7-yl-amino)-ethanone (45 70002104)

The title compound is prepared from 7-amino-4H-benzo[1,4]oxazine-3-one and 2-chloro-1-(4-benzyl-piperidin-1-yl)-ethanone (Example 200a) according to the method described in Example 142b. Mp.: 172-175 °C (diethylether).

Example 89

1-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-2-(1H-indazol-6-yl-amino)-ethanone (45 70001817)

The title compound is prepared from 6-aminoindazol and 2-chloro-1-[4-(4-fluoro-benzyl)-piperidin-1-yl]-ethanone (Example 197a) according to the method described in Example 142b. Mp.: 181-183 °C (diethylether)

Example 90

1-(4-Benzyl-piperidin-1-yl)-2-(1H-indazol-6-yl-amino)-ethanone (45 70001950)

The title compound is prepared from 6-aminoindazol and 2-chloro-1-(4-benzyl-piperidin-1-yl)-ethanone (Example 200a) according to the method described in Example 142b. Mp.: 179-182 °C (diethylether)

Example 91

1-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl-amino)-ethanone (45 70002176)

The title compound is prepared from 6-amino-4H-benzo[1,4]oxazin-3-one and 2-chloro-1-[4-(4-fluoro-benzyl)-piperidin-1-yl]-ethanone (Example 197a) according to the method described in Example 142b. Mp.: 220-223 °C (diethylether)

Example 92

N-(4-{2-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-2-oxo-ethylamino}-phenyl)-metanesulfonamide (45 70002491)

A mixture of 1.08g (4 mmol) of 2-chloro-1-[4-(4-fluoro-benzyl)-piperidin-1-yl]-ethanone (Example 197a), 1.5 g (8 mmol) of methanesulfonic acid-(4-amino-anilide), 0.68 g (4 mmol) of potassium iodide, 1.2 ml (8 mmol) of triethylamine and 40 ml of toluene is refluxed for 3 h. The reaction mixture is concentrated and 30 ml of water and 30 ml of chloroform are added to the residue The organic layer is separated and the water phase is extracted three times with 10 ml of chloroform. The combined organic layers are dried over sodium sulfate. Concentrated and the residue is purified by column chromatography using Kieselgel 60 adsorbent (Merck) and chloroform:methanol = 99:1 as eluent to yield 0.96 g (57 %) of the title compound. Mp.: 177-181 °C (diisopropylether)

Example 93

1-(4-Benzyl-piperidin-1-yl)-2-(2-oxo-2,3-dihydro-benzothiazol-6-yl-amino)-ethanone (45 70003033)

The title compound is prepared from 6-amino-3H-benzothiazole-2-one and 2-chloro-1-(4-benzyl-piperidin-1-yl)-ethanone (Example 200a) according to the method described in Example 206. Mp.: 196-199 °C (diethylether)

Example 94

1-(4-p-Tolyloxy-piperidin-1-yl)-2-(2-oxo-2,3-dihydro-benzothiazol-6-yl-amino)-ethanone (45 70003072)

208a) 2-chloro-1-(4-p-tolyloxy-piperidin-1-yl)-ethanone

The title compound is prepared from 4-p-tolyloxy-piperidine and chloroacetyl chloride according to the method described in Example 142a. Mp.: oil

208b) 1-(4-p-Tolyloxy-piperidin-1-yl)-2-(2-oxo-2,3-dihydro-benzothiazole-6-yl-amino)-ethanone

The title compound is prepared from 6-amino-3H-benzothiazole-2-one and 2-chloro-1-(4-p-tolyloxy-piperidin-1-yl)-ethanone according to the method described in Example 206. Mp.: 189-191 °C (diethylether)

Example 95

2-(4-p-Tolyloxy-piperidin-1-yl)-2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl-amino)-ethanone (45 70003118)

The title compound is prepared from 7-amino-4H-benzo[1,4]oxazin-3-one and 2-chloro-1-(4-p-tolyloxy-piperidin-1-yl) ethanone (Example 208a) according to the method described in Example 206. Mp.: 223-224 °C (diethylether)

Example 96

1-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-2-(2-oxo-2,3-dihydro-benzothiazol-6-yl-amino)-ethanone (45 70003032)

The title compound is prepared from 6-amino-3H-benzothiazol-2-one and 2-chloro-1-[4-(4-fluoro-benzyl)-piperidin-1-yl]-ethanone (Example 197a) according to the method described in Example 206. Mp.: 149-155 °C (diethylether)

Example 97

5-{2-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-2-(2-oxo-ethylamino}-1,3-dihydro-indol-2-one (45 70002509)

The title compound is prepared from 5-amino-1,3-dihydro-indol-2-one and 2-chloro-1-[4-(4-fluoro-benzyl)-piperidin-1-yl]-ethanone (Example 197a) according to the method described in Example 206. Mp.: 161-164 °C (diethylether)

Example 98

5-[2-[4-Benzyl)-piperidin-1-yl)-2-oxo-ethylamino]-1,3-dihydro-indol-2-one (45 70002642)

The title compound is prepared from 5-amino-1,3-dihydro-indol-2-one and 2-chloro-1-(4-benzyl-piperidin-1-yl)-ethanone (Example 200a) according to the method described in Example 206. Mp.: 155-160 °C (diethylether)

Example 99

6-{2-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-2-oxo-ethylamino}-3H-benzoxazol-2-one hydrochloride (45 70002862)

The title compound is prepared from 6-{2-[4-(4-fluoro-benzyl)-piperidin-1-yl]-2-oxoethylamino}-3H-benzoxazol-2-one (Example 198) according to the method described in Example 194. Mp.: 180-210 °C (dec.) (ethyl acetate)

Example 100

5-[2-(4-Benzyl-piperidin-1-yl)-2-oxo-ethylamino]-1,3-dihydro-benzimidazol-2-one (45 70002223)

The title compound is prepared from 5-amino-1,3-dihydro-benzimidazol-2-one and 2-chloro-1-(4-benzyl-piperidin-1-yl)-ethanone (Example 200a) according to the method described in Example 142b. Mp.: 237-238 °C (diethylether)

Example 101

5-[2-(4-Benzyl-piperidin-1-yl)-2-oxo-ethylamino]-1,3-dihydro-benzoimidazol-2-one hydrochloride (45 70002907)

The title compound is prepared from 5-[2-(4-benzyl-piperidin-1-yl)-2-oxo-ethylamino]-1,3-dihydro-bezimidazol-2-one (Example 224) according to the method described in Example 194. Mp.: 215-230 °C (dec.) (ethyl acetate)

Example 102

5-{2-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-2-oxo-ethylamino}-1,3-dihydro-benzimidazol-2-one hydrochloride (45 70002908

The title compound is prepared from 5-{2-[4-(4-fluoro-benzyl)-piperidin-1-yl]-2-oxo-ethylamino}-1,3-dihydro-benzimidazol-2-one (Example 197b) according to the method described in Example 194. Mp.: 217-229 °C (dec.) (ethyl acetate)

Example 103

N-(4-{2-[4-(4-Methyl-benzyl)-piperidin-1-yl]-2-oxo-ethylamino}-phenyl)-methane-sulfonamide (45 70002955)

227a) 2-Chloro-1-[4-(4-methyl-benzyl)-piperidin-1-yl]-ethanone

The title compound is prepared from 4-(4-methyl-benzyl)-piperidine and chloroacetyl chloride according to the method described in Example 142a. Mp.: oil.

227b) N-(4-{2-[4-(4-Methyl-benzyl)-piperidin-1-yl]-2-oxo-ethylamino}-phenyl)-methane-sulfonamide

The title compound is prepared from 2-chloro-1-[4-(4-methyl-benzyl)-piperidin-1-yl]-ethanone and methanesulfonic acid-(4-aminoanilide) according to the method described in Example 206. Mp.: 133-135 °C (diisopropylether)

Example 104

6-{2-[4-(4-Methyl-benzyl)-piperidin-1-yl]-2-oxo-ethylamino}-3H-benzoxazol-2-one (45 70002956)

The title compound is prepared from 2-chloro-1-[4-(4-methyl-benzyl)-piperidin-1-yl]-ethanone (Example 227a) and 6-amino-3H-benzoxazol-2-one according to the method described in Example 206. Mp.: 212-215 °C (methanol)

Example 105

7-{2-[4-(4-Methyl-benzyl)-piperidin-1-yl]-2-oxo-ethylamino}-4H-benzo[1,4]oxazin-3-one (45 70003022)

The title compound is prepared from 2-chloro-1-[4-(4-methyl-benzyl)-piperidin-1-yl]-ethanone (Example 227a) and 7-amino-4H-benzo[1,4]oxazine-3-one according to the method described in Example 206. Mp.: 206-208 °C (ethanol)

Example 106

6-[2-(4-Benzyl-piperidin-1-yl)-2-oxo-ethylamino]-3H-benzoxazol-2-one

(45 70002530)

The title compound is prepared from 6-amino-3H-benzoxazol-2-one and 2-chloro-1-(4-benzyl-piperidin-1-yl)-ethanone (Example 200a) according to the method described in Example 142b. Mp.: 204-206 °C (diethylether)

Example 107

6-[2-(4-Benzyl-piperidin-1-yl)-2-oxo-ethylamino]-3,4-dihydro-1H-quinolin-2-one

(45 70003105)

The title compound is prepared from 6-amino-3,4-dihydro-1H-quinoline-2-one and 2-chloro-1-(4-benzyl-piperidin-1-yl)-ethanone (Example 200a) according to the method described in Example 206. Mp.: 184-187 °C (ethanol)

Example 108

6-{2-[4-(4-Chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethylamino}-3H-benzoxazol-2-one (45 70003134)

233a) 2-Chloro-1-[4-(4-chloro-phenoxy)-piperidin-1-yl]-ethanone

The title compound is prepared from 4-(4-chloro-phenoxy)-piperidine hydrochloride (Example 30b) and chloroacetyl chloride according to the method described in Example 142a. Mp.: oil

233b) 6-{2-[4-(4-Chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethylamino}-3H-benzoxazol-2-one

The title compound is prepared from 6-amino-3H-benzoxazol-2-one and 2-chloro-1-[4-(4-chloro-phenoxy)-piperidin-1-yl]-ethanone according to the method described in Example 206. Mp.: 180-183 °C (diethylether)

Example 109

6-{2-[4-(4-Chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethylamino}-3,4-dihydro-1H-quinolin-2-one (45 70003135)

The title compound is prepared from 6-amino-3,4-dihydro-quinolin-2-one and 2-chloro-1-[4-(4-chloro-phenoxy)-piperidin-1-yl]-ethanone (Example 233a) according to the method described in Example 206. Mp.: 248-251 °C (diethylether)

Example 110

5-{2-[4-(4-Chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethylamino}-1,3-dihydro-benzoimidazol-2-one (45 70003137)

The title compound is prepared from 5-amino-1,3-dihydro-benzimidazol-2-one and 2-chloro-1-[4-(4-chloro-phenoxy)-piperidin-1-yl]-ethanone (Example 233a) according to the method described in Example 206. Mp.: 201-205 °C (diethylether)

Example 111

6-{2-[4-(4-Fluoro-benzyl)-piperidin-1-yl]-2-oxo-ethylamino}-3,4-dihydro-1H-quinolin-2-one (45 70003136)

The title compound is prepared from 6-amino-3,4-dihydro-quinolin-2-one and 2-chloro-1-[4-(4-fluoro-benzyl)-piperidin-1-yl]-ethanone (Example 197a) according to the method described in Example 206. Mp.: 197-200 °C (ethyl alcohol)

Example 112

6-[2-(4-Benzyl-piperidin-1-yl)-1-methyl-2-oxo-ethylamino]-3H-benzoxazol-2-one (45 70002184)

238a) 1-(4-Benzyl-piperidine-1-yl)-2-bromo-propan-1-one

The title compound is prepared from 4-benzyl-piperidine and 2-bromo-propionyl chloride according to the method described in Example 142a. Mp.: oil.

238b) 6-[2-(4-Benzyl-piperidin-1-yl)-1-methyl-2-oxo-ethylamino]-3H-benzoxazol-2-one

A mixture of 1.03 g (3.33 mmol) of 1-(4-benzyl-piperidine-1-yl)-2-bromo-propan-1-one, 0.5 g (3.33 mmol) of 6-amino-3H-benzoxazol-2-one, 1.0 g (7.2 mmol) of potassium carbonate and 15 ml of dimethylformamide is refluxed for 5 h. The reaction mixture is filtered and the filtrate is concentrated. The residue is purified by column chromatography using Kieselgel 60 adsorbent (Merck) and hexane:ethyl acetate = 4:1 as eluent to yield 0.46 g (36.5 %) of the title compound. Mp.: 91 °C (hexane)

Example 113

2-(3-Benzyl-8-aza-biciklo[3.2.1]oct-8-yl)-2-oxo-N-(2-oxo-2,3-dihydro-1H-indole-5-yl)-acetamide (45 70002703)

The title compound is prepared from N-(2-oxo-2,3-dihydro-1H-indole-5-yl)-oxalamic acid (Example 101b) and 3-benzyl-8-aza-bicyclo[3.2.1]octane [WO 20132179] according to the method described in Example 1c. Mp.: 197.5-200 °C (diethylether)

Example 114

2-(4-Benzyl-piperidin-1-yl)-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-5-yl)-acetamide (45 70001830)

The title compound is prepared from 5-amino-3H-benzoxazole-2-one and (4-benzyl-piperidin-1-yl)-oxo-acetic acid (Example 5b) according to the method described in Example 2. Mp.: 187-190 °C (water)

Example 115

2-[4-(4-Hydroxy-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide (45 70003208)

The title compound is prepared from 2-[4-(4-methoxy-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide (Example 122) according to the method described in Example 192. Mp.:235-239 °C (diethylether)

Example 116

7-{2-[4-(4-Chloro-phenoxy)-piperidin-1-yl]-2-oxo-ethylamino}-4H-benzo[1,4]oxazin-3-one (45 70003085)

The title compound is prepared from 2-chloro-1-[4-(4-chloro-phenoxy)-piperidin-1-yl]-ethanone (Example 233) and 7-amino-4H-benzo[1,4]oxazin-3-one according to the method described in Example 206. Mp.:207-210 °C (methanol)

Example 117

6-[2-Oxo-2-(4-phenoxy-piperidin-1-yl)-ethylamino]-3H-benzoxazol-2-one (45 70003156)

244a) 2-Chloro-1-(4-phenoxy-piperidin-1-yl)-ethanone

The title compound is prepared from 4-phenoxy-piperidine and chloroacetyl chloride according to the method described in Example 142a. Mp.: oil

244bb) 6-[2-Oxo-2-(4-phenoxy-piperidin-1-yl)-ethylamino]-3H-benzoxazol-2-one

The title compound is prepared from 2-chloro-1-(4-phenoxy)-piperidin-1-yl]-ethanone and 6-amino-3H-benzoxazol-2-one according to the method described in Example 206. Mp.:220-223 °C (diethylether)

Example 118

2-(4-Benzyl-piperidin-1-yl)-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-acetamide (45 70001712)

118a) 2-Chloro-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-acetamide

The title compound is prepared from 5-amino-1,3-dihydro-indol-2-one and chloroacetyl chloride according to the method described in Example 81a. Mp.: 166-170 °C (water)

118b) 2-(4-Benzyl-piperidin-1-yl)-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-acetamide

A mixture of 0.9 g (4 mmol) of 2-chloro-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-acetamide, 0.7 g (4 mmol) of potassium iodide, 0.6 ml (4 mmol) of triethylamine, 0.53 ml (3 mmol) of 4-benzyl-piperidine and 50 ml of acetonitrile is refluxed for 20 h. The reaction mixture is concentrated and 30 ml of water and 30 ml of chloroform are added to the residue. The organic layer is separated and the water phase is extracted three times with 10 ml of chloroform. The combined organic layers are dried over sodium sulfate, concentrated and the residue is treated with diethylether and the precipitated crystals are filtered off to yield 0.7 g (64 %) of the title compound. Mp.: 176-180 °C (diethylether)

Example 119

2-(4-Benzyl-piperidin-1-yl)-N-(4-methoxy-phenyl)-acetamide (45 70002794)

The title compound is prepared from 2-chloro-N-(4-methoxy-phenyl)-acetamide [J. Heterocycl. Chem., **32,** 1429. (1995)] and 4-benzyl-piperidine according to the method described in Example 118b. Mp.: 81-83 °C (hexane)

Example 120

2-(4-Benzyl-piperidin-1-yl)-N-(4-hydroxy-phenyl)-acetamide (45 70002863)

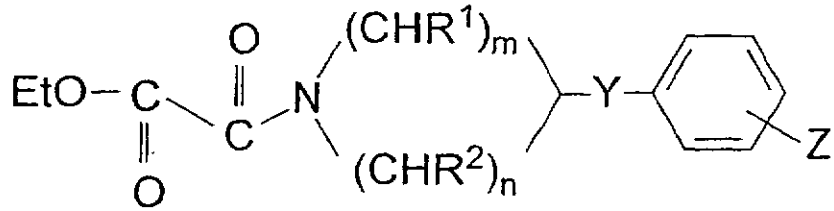
To a stirred solution of 0.68 g (2 mmol) of 2-(4-benzyl-piperidin-1-yl)-N-(4-methoxy-phenyl)-acetamide (Example 119) and in 30 ml of dichloromethane 0.95 ml (10 mmol) of boron tribromide in 9 ml of dichloromethane is added dropwise at -20 °C, and the reaction mixture is stirred at room temperature for 10 h. The reaction mixture is concentrated. Then 30 ml of 8 % sodium hydrogenecarbonate solution and 20 ml of chloroform are added to the mixture. The organic layer is separated and the water phase is extracted three times with 20 ml of chloroform. The combined organic layers are dried over sodium sulfate, concentrated and the residue is purified by column chromatography using Kieselgel 60 as adsorbent (Merck) and chloroform : methanol = 9:1 as eluent to yield 0.4 g (62 %) of the title compound. Mp.: 66-70 °C (hexane)

Example 121

Procedure "A"

for producing compound of formula (I), where X mean -CO- group and R^1, R^2, Y, Z, U, V, n and m are as defined for the formula (I).

Step (1): Preparation of the ester compounds of formula (VIII)

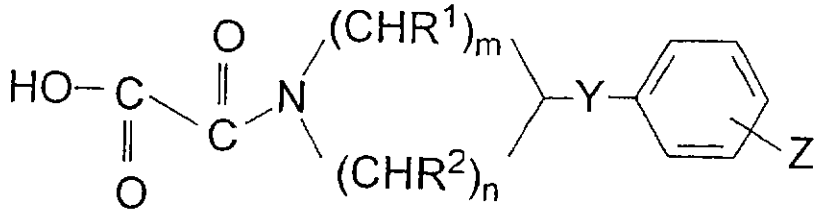


(VIII)

where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I).

0.1 mmol of a secondary amines of formula (III) - where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I) - are solved in 0.4 ml of CH_2Cl_2. Solid-supported base 2.5 (diisopropylaminomethylpolystyrene, 3 mmol/g, Fluka, cat.nr.: 38343) (83 mg) and 11.2 µL of ethyl oxalylchloride are added to the solution. The mixture is vigorously shaken for 2 hours at 40 °C. The slurry is filtered off, and the resin is washed 3 times with CH_2Cl_2. The filtrate is concentrated in vacuum. (yield: ~100 %)

Step (2): Hydrolysis of the above ester compounds to oxalic acid monoamides of formula (IX)



(IX)

where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I).

The above obtained ester compounds of formula (VIII) are solved in 0.8 ml of ethanol and 120 mg of strongly basic ion exchange resin (DOWEX-2X8-100) in OH^- form is added. The mixture is vigorously shaken for 16 hours at 60 °C, then the solvent is filtered off. The resin is washed 3 times with ethanol. The resin then suspended in 0.8 ml of ethyl acetate, 0.8 ml of 1.5 M HCl / ethyl acetate is added and the mixture is vigorously shaken for 3 hours at room temperature. The resin is filtered off, washed with ethyl acetate and the filtrate is concentrated in vacuum. (yield: ~ 100 %)

Step (3): Coupling

The above obtained oxalic acid monoamides of formula (IX) are solved in 2 ml of CH_2Cl_2 / DMF 1:1. 0.125 mmol of amine of formula (V) - where V and U mean as given for formula (I) - and 0.25 mmol of 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide (EDC) are added and the mixture is vigorously shaken for 12 hours. The mixture is diluted with 2 ml of CH_2Cl_2, and extracted with 4 mL of water three times. Solid supported 4-benzyloxybenzaldehyde (200 mg, 3 mmol/g, Novabiochem, Cat.nr.: 01-64-0182) is added to the organic solution and the mixture is vigorously shaken for 2 hours at 40 °C. The resin is filtered off and the filtrate is concentrated to yield as final product the compounds of formula (I) - where X mean -CO- group and R^1, R^2, Y, Z, U, V, n and m are as defined above.

Example 122

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 quadruple 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 compounds prepared as described above in procedures "A" and "B" are shown in Tables 3, 4, 5 and 6, respectively.

Table 3

Compounds of formula (I) prepared by procedure "A" described in Example 259 where X means -CO- group, both of $-(CHR^1)_m-$ and $-(CHR^2)_n-$ are $-CH_2-CH_2-$ groups, Y, Z, U and V are as given below:

No.	V	U	Y	Z	MW_c	MW_f	k'
1.	4- Ac-NH-	H-	$-CH_2-$	4-F-	397.45	398.5	3.421
2.	4- Ac-NH-	H-	$-CH_2-$	4-Cl-	413.905	414.5	3.202
3.	4- CH_3-SO_2-NH-	H-	-O-	$4-CH_3-$	431.507	432.5	3.349
4.	4- Ac-NH-	H-	-O-	$4-CH_3-$	395.459	396.4	3.306
5.	4- CH_3-SO_2-NH-	H-	-O-	4-Cl-	451.925	452.5	3.545
6.	4- CH_3-SO_2-NH-	H-	$-CH_2-$	4-Cl-	449.953	450.4	3.67
7.	4- Ac-NH-	H-	-O-	4-Cl-	415.877	416.5	3.518
8.	4- CH_3-SO_2-NH-	H-	$CH_3-N<$	4-Cl-	464.968	465.5	2.304
9.	4- Ac-NH-	H-	$CH_3-N<$	4-Cl-	428.92	429.5	2.259
10.	4- CH_3-SO_2-NH-	H-	$-CH_2-CH_2-$	4-F-	447.525	448.5	3.57
11.	4- Ac-NH-	H-	$-CH_2-CH_2-$	4-F-	411.477	412.5	3.555
12.	4- CH_3-SO_2-NH-	H-	$CH_3-N<$	$4-CH_3-$	444.55	445.5	1.155
13.	4- CH_3-SO_2-NH-	H-	$-CH_2-N(CH_3)-$	H-	444.55	445.4	1.776
14.	4- Ac-NH-	H-	$CH_3-N<$	4-Br-	473.371	474.4	2.33
15.	4- Ac-NH-	H-	$CH_3-N<$	$4-CH_3-$	408.502	409.5	2.169

Table 4

Compounds of formula (I) prepared by procedure "A" described in Example 259 where X means -CO- group, both of $-(CHR^1)_m-$ and $-(CHR^2)_n-$ are $-CH_2-CH_2-$ groups, U and V form together a bivalente group and Y and Z are as given below:

No.	V + U	Y	Z	MW_c	MW_f	k'
1.	3-4 -N=N-NH-	$-CH_2-$	4-F-	381.411	382.1	3.387
2.	3-4 -NH-CO-NH-	$-CH_2-$	4-CH_3-	392.459	393.1	3.386
3.	3-4 -O-CH_2-CO-NH-	$-CH_2-$	4-Cl-	427.888	428.5	3.691
4.	3-4 -N=N-NH-	$-CH_2-$	4-Cl-	397.866	398.5	3.592
5.	3-4 -CH_2-CH_2-CO-NH-	$-CH_2-$	4-Cl-	425.916	426.6	3.679
6.	3-4 -CH=N-NH-	-O-	4-CH_3-	378.432	379.5	3.385
7.	3-4 -CH=CH-NH-	-O-	4-CH_3-	377.444	378.5	3.55
8.	3-4 -CH_2-CH_2-CO-NH-	-O-	4-CH_3-	407.47	408.5	3.366
9.	3-4 -CH=CH-NH-	$-CH_2-$	4-F-	379.435	380.1	3.645
10.	3-4 -NH-CO-O-	$-CH_2-$	4-CH_3-	393.443	394.5	3.588
11.	3-4 -CH=N-NH-	$-CH_2-$	4-CH_3-	376.46	377.5	3.631
12.	3-4 -CH=CH-NH-	$-CH_2-$	4-CH_3-	375.472	376.5	3.78
13.	3-4 -N=N-NH-	$-CH_2-$	4-CH_3-	377.448	378.5	3.533
14.	3-4 -CH_2-CH_2-CO-NH-	$-CH_2-$	4-CH_3-	405.498	406.5	3.612
15.	3-4 -NH-CO-O-	-O-	4-Cl-	415.833	416.4	3.48
16.	3-4 -O-CH_2-CO-NH-	-O-	4-Cl-	429.86	430.5	3.516
17.	3-4 -CH_2-CH_2-CO-NH-	$-CH_2-$	4-F-	409.461	410.6	3.47
18.	3-4 -CH=N-NH-	$-CH_2-$	4-Cl-	396.878	397.4	3.697
19.	3-4 -CH=CH-NH-	$-CH_2-$	4-Cl-	395.89	396.5	3.839
20.	3-4 -CH=N-NH-	-O-	4-Cl-	398.85	399.5	3.523
21.	3-4 -CH=CH-NH-	-O-	4-Cl-	397.862	398.3	3.679
22.	3-4 -N=N-NH-	-O-	4-Cl-	399.838	400.6	3.422
23.	3-4 -CH_2-CH_2-CO-NH-	-O-	4-Cl-	427.888	428.5	3.504
24.	3-4 -N=N-NH-	-O-	4-CH_3-	379.42	380.1	3.281
25.	3-4 -NH-CO-O-	CH_3-N<	4-Cl-	428.876	429.5	2.37
26.	3-4 -NH-CO-NH-	CH_3-N<	4-Cl-	427.892	428.6	2.179
27.	3-4 -N=CH-NH-	CH_3-N<	4-Cl-	411.893	412.5	1.811
28.	3-4 -O-CH_2-CO-NH-	CH_3-N<	4-Cl-	442.903	443.5	2.39
29.	3-4 -CH=N-NH-	CH_3-N<	4-Cl-	411.893	412.5	2.359
30.	3-4 -N=N-NH-	CH_3-N<	4-Cl-	412.881	413.5	2.295

31.	3-4 -CH_2-CH_2-CO-NH-	CH_3-N<	4-Cl-	440.931	441.5	2.382
32.	3-4 -NH-CO-CO-NH-	CH_3-N<	4-Cl-	455.902	456.5	2.161
33.	3-4 -S-CO-NH-	-CH_2-	4-CH_3-	409.52	410.5	3.693
34.	3-4 -S-CO-NH-	-CH_2-	4-Cl-	429.93	430.4	3.751
35.	3-4 -NH-CS-NH-	-O-	4-CH_3-	410.5	411.5	3.155
36.	3-4 -S-CO-NH-	-O-	4-CH_3-	411.49	412.5	3.462
37.	3-4 -NH-CS-NH-	CH_3-N<	4-Cl-	443.96	444.5	2.250
38.	3-4 -S-CO-NH-	CH_3-N<	4-Cl-	444.95	445.5	2.55
39.	3-4 -NH-CO-O-	-CH_2-CH_2-	4-F-	411.433	412.5	3.56
40.	3-4 -N=CH-NH-	-CH_2-CH_2-	4-F-	394.45	395.5	3.028
41.	3-4 -O-CH_2-CO-NH-	-CH_2-CH_2-	4-F-	425.46	426.5	3.629
42.	3-4 -CH=N-NH-	-CH_2-CH_2-	4-F-	394.45	395.5	3.609
43.	3-4 -N=N-NH-	-CH_2-CH_2-	4-F-	395.438	396.5	3.517
44.	3-4 -CH_2-CH_2-CO-NH-	-CH_2-CH_2-	4-F-	423.488	424.5	3.591
45.	3-4 -NH-CS-NH-	-CH_2-CH_2-	4-F-	426.52	427.5	3.448
46.	3-4 -S-CO-NH-	-CH_2-CH_2-	4-F-	427.51	428.5	3.721
47.	3-4 -NH-CO-O-	CH_3-N<	4-CH_3-	408.458	409.5	2.244
48.	3-4 -N=CH-NH-	CH_3-N<	4-CH_3-	391.475	392.5	1.711
49.	3-4 -O-CH_2-CO-NH-	CH_3-N<	4-CH_3-	422.485	423.5	2.264
50.	3-4 -CH=N-NH-	CH_3-N<	4-CH_3-	391.475	392.5	2.237
51.	3-4 -N=N-NH-	CH_3-N<	4-CH_3-	392.463	393.5	2.165
52.	3-4 -NH-C(CH_3)=N-	CH_3-N<	4-CH_3-	405.502	406.5	1.813
53.	3-4 -CH_2-CH_2-CO-NH-	CH_3-N<	4-CH_3-	420.513	421.6	2.265
54.	3-4 -NH-CS-NH-	CH_3-N<	4-CH_3-	423.55	424.5	2.149
55.	3-4 -S-CO-NH-	CH_3-N<	4-CH_3-	424.53	425.5	2.439
56.	3-4 -NH-CS-NH-	-CH_2-	4-F-	412.5	413.5	3.376
57.	3-4 -S-CO-NH-	-CH_2-	4-F-	413.5	414.5	3.562
58.	3-4 -NH-CS-NH-	-CH_2-	4-Cl-	428.95	429.4	3.477
59.	3-4 -S-CO-NH-	-O-	4-Cl-	431.91	432.4	3.582
60.	3-4 -CH=CH-NH-	-CH_2-CH_2-	4-F-	393.462	394.5	3.74
61.	3-4 -CH=CH-NH-	CH_3-N<	4-Cl-	410.905	411.5	2.502

62.	3-4 -NH-CO-O-	$-CH_2-N(CH_3)-$	H-	408.458	409.4	1.882
63.	3-4 $-O-CH_2-CO-NH-$	$-CH_2-N(CH_3)-$	H-	422.485	423.5	1.925
64.	3-4 -CH=CH-NH-	$-CH_2-N(CH_3)-$	H-	390.487	391.4	1.945
65.	3-4 -NH-CS-NH-	$-CH_2-N(CH_3)-$	H-	423.535	424.5	1.834
66.	3-4 -S-CO-NH-	$-CH_2-N(CH_3)-$	H-	424.519	425.5	2.108
67.	3-4 -NH-CO-O-	$CH_3-N<$	4-Br-	473.327	474.3	2.404
68.	3-4 -NH-CO-NH-	$CH_3-N<$	4-Br-	472.343	473.4	2.218
69.	3-4 -N=CH-NH-	$CH_3-N<$	4-Br-	456.344	457.4	1.839
70.	3-4 $-O-CH_2-CO-NH-$	$CH_3-N<$	4-Br-	487.354	488.4	2.428
71.	3-4 -CH=CH-NH-	$CH_3-N<$	4-Br-	455.356	456.4	2.539
72.	3-4 $-CH_2-CH_2-CO-NH-$	$CH_3-N<$	4-Br-	485.382	486.4	2.429

Table 5

Compounds of formula (I) prepared by procedure "B" described in Example 260 where X means $-CH_2-$ group, both of $-(CHR^1)_m-$ and $-(CHR^2)_n-$ are $-CH_2-CH_2-$ groups Y, Z, U and V are as given below:

No.	V	U	Y	Z	MW_c	MW_f	k'
1.	4- Ac-NH-	H-	$-CH_2-$	H-	365.477	366.5	2.272
2.	4- CH_3-SO_2-NH-	H-	$-CH_2-$	4-F-	419.515	420.5	2.335
3.	4- Ac-NH-	H-	$-CH_2-$	4-F-	383.467	384.5	2.366
4.	4- HO-	H-	$-CH_2-$	4-F-	342.413	343.5	2.100
5.	4- Ac-NH-	H-	$-CH_2-$	4-Cl-	399.922	400.5	2.644
6.	4- CH_3-SO_2-NH-	H-	$-CH_2-$	4-Cl-	435.97	436.5	2.649
7.	4- HO-	H-	$-CH_2-$	4-Cl-	358.869	359.4	2.48
8.	4- CH_3-SO_2-NH-	H-	-O-	4-Cl-	437.942	438.4	2.455
9.	4- Ac-NH-	H-	-O-	4-Cl-	401.894	402.5	3.35
10.	4- HO-	H-	-O-	4-Cl-	360.841	361.4	2.264
11.	4- Ac-NH-	H-	-O-	$4-CH_3-$	381.476	382.5	2.329
12.	4- HO-	H-	-O-	$4-CH_3-$	340.423	341.4	2.112
13	4- CH_3-SO_2-NH-	H-	$-CH_2-$	$4-CH_3-$	415.552	416.6	2.539

14	4- Ac-NH-	H-	$-CH_2-$	4-CH_3-	379.504	380.5	2.527
15.	4- HO-	H-	$-CH_2-$	4-CH_3-	338.451	339.5	2.33
16.	4- HO-	H-	$CH_3-N<$	4-Cl-	373.884	374.4	1.369
17.	4- Ac-NH-	H-	$CH_3-N<$	4-Cl-	414.937	415.4	1.785
18.	4- CH_3-SO_2-NH-	H-	$CH_3-N<$	4-Cl-	450.985	451.5	1.704
19.	4- CH_3-SO_2-NH-	H-	$-CH_2-CH_2-$	4-F-	433.542	434.3	2.504
20.	4- Ac-NH-	H-	$-CH_2-CH_2-$	4-F-	397.494	398.2	2.53
21.	4- HO-	H-	$-CH_2-CH_2-$	4-F-	356.441	357.2	2.325
22.	4- CH_3-SO_2-NH-	H-	$CH_3-N<$	4-CH_3-	430.567	431.3	1.332
23.	4- Ac-NH-	H-	$CH_3-N<$	4-CH_3-	394.519	395.3	1.433
24.	4- Ac-NH-	H-	$CH_3-N<$	4-Br-	459.388	460.2	1.864
25.	4- HO-	H-	$CH_3-N<$	4-Br-	418.335	419.2	1.461
26.	4- CH_3-SO_2-NH-	H-	$CH_3-N<$	4-Br-	495.436	496.3	1.793
27.	4- HO-	H-	$CH_3-N<$	4-CH_3-	353.466	354.3	1.027

Table 6

Compounds of formula (I) prepared by procedure "B" described in Example 260 where X means $-CH_2-$ group, both of $-(CHR^1)_m-$ and $-(CHR^2)_n-$ are $-CH_2-CH_2-$ groups, U and V form together a bivalente group and Y and Z are as given below:

No.	V + U	Y	Z	MW_e	MW_f	k'
1.	3-4 -NH-CO-O-	$-CH_2-$	H-	365.433	366.4	2.297
2.	3-4 -N=CH-NH-	$-CH_2-$	H-	348.45	349.4	1.708
3.	3-4 -NH-N=CH-	$-CH_2-$	H-	348.45	349.4	2.392
4.	3-4 -CH=N-NH-	$-CH_2-$	H-	348.45	349.4	2.36
5.	3-4 -CH=CH-NH-	$-CH_2-$	H-	347.462	348.4	2.449
6.	3-4 -N=N-NH-	$-CH_2-$	H-	349.438	350.4	2.286
7.	3-4 -S-C(SH)=N-	$-CH_2-$	H-	397.555	398.4	2.729
8.	3-4 -CH=C(CH_3)-NH-	$-CH_2-$	H-	361.489	362.5	2.656
9.	3-4 -NH-C(CH_3)=N-	$-CH_2-$	H-	362.477	363.5	1.849
10.	3-4 $-CH_2-CH_2-$CO-NH-	$-CH_2-$	H-	377.488	378.5	2.376
11.	3-4 -S-CO-NH-	$-CH_2-$	H-	381.494	382.5	2.516

12.	3-4 -NH-CO-O-	$-CH_2-$	4-F-	383.423	384.4	2.408
13.	3-4 -N=CH-NH-	$-CH_2-$	4-F-	366.44	367.5	1.808
14.	3-4 -O-CH_2-CO-NH-	$-CH_2-$	4-F-	397.45	398.5	2.445
15.	3-4 -NH-N=CH-	$-CH_2-$	4-F-	366.44	367.5	2.483
16.	3-4 -CH=N-NH-	$-CH_2-$	4-F-	366.44	367.5	2.446
17.	3-4 -CH=CH-NH-	$-CH_2-$	4-F-	365.452	366.5	2.558
18.	3-4 -N=N-NH-	$-CH_2-$	4-F-	367.428	368.5	2.381
19.	3-4 -S-C(SH)=N-	$-CH_2-$	4-F-	415.545	416.5	2.788
20.	3-4 -CH=C(CH_3)-NH-	$-CH_2-$	4-F-	379.479	380.5	2.743
21.	3-4 -NH-C(CH_3)=N-	$-CH_2-$	4-F-	380.467	381.5	1.942
22.	3-4 -CH_2-CH_2-CO-NH-	$-CH_2-$	4-F-	395.478	396.5	2.455
23.	3-4 -NH-CS-NH-	$-CH_2-$	4-F-	398.5	399.5	2.349
24.	3-4 -S-CO-NH-	$-CH_2-$	4-F-	399.484	400.4	1.59
25.	3-4 -N=CH-NH-	$-CH_2-$	4-CH_3-	362.477	363.5	2.002
26.	3-4 -O-CO-NH-	$-CH_2-$	4-Cl-	399.878	400.4	2.687
27.	3-4 -NH-CO-O-	$-CH_2-$	4-Cl-	399.878	400.4	2.669
28.	3-4 -CH=CH-NH-	$-CH_2-$	4-Cl-	381.907	382.5	2.827
29.	3-4 -S-C(SH)=N-	$-CH_2-$	4-Cl-	432.00	432.4	3.006
30.	3-4 -CH=C(CH_3)-NH-	$-CH_2-$	4-Cl-	395.934	396.5	2.972
31.	3-4 -NH-C(CH_3)=N-	$-CH_2-$	4-Cl-	396.922	397.5	2.222
32.	3-4 -CH_2-CH_2-CO-NH-	$-CH_2-$	4-Cl-	411.933	412.5	2.727
33.	3-4 -CH_2-CO-NH-	$-CH_2-$	4-Cl-	397.906	398.5	2.616
34.	3-4 -N=CH-NH-	$-CH_2-$	4-Cl-	382.895	383.5	2.154
35.	3-4 -O-CH_2-CO-NH-	$-CH_2-$	4-Cl-	413.905	414.5	2.724
36.	3-4 -NH-CS-NH-	$-CH_2-$	4-Cl-	414.955	415.4	2.616
37.	3-4 -S-CO-NH-	$-CH_2-$	4-Cl-	415.939	416.4	2.105
38.	3-4 -O-CO-NH-	-O-	4-Cl-	401.85	402.4	2.513
39.	3-4 -NH-CO-O-	-O-	4-Cl-	401.85	402.4	2.481
40.	3-4 -N=CH-NH-	-O-	4-Cl-	384.867	385.5	1.93
41.	3-4 -O-CH_2-CO-NH-	-O-	4-Cl-	415.877	416.4	2.54
42.	3-4 -NH-N=CH-	-O-	4-Cl-	384.867	385.4	2.575

43.	3-4 -CH=N-NH-	-O-	4-Cl-	384.867	385.4	2.544
44.	3-4 -CH=CH-NH-	-O-	4-Cl-	383.879	384.4	2.646
45.	3-4 -CH=C(CH_3)-NH-	-O-	4-Cl-	397.906	398.5	2.807
46.	3-4 -NH-C(CH_3)=N-	-O-	4-Cl-	398.894	399.4	2.058
47.	3-4 -CH_2-CH_2-CO-NH-	-O-	4-Cl-	413.905	414.5	2.56
48.	3-4 -S-CO-NH-	-O-	4-Cl-	417.911	418.4	2.677
49.	3-4 -O-CO-NH-	-O-	4-CH_3-	381.432	382.4	2.391
50.	3-4 -NH-CO-O-	-O-	4-CH_3-	381.432	382.5	2.374
51.	3-4 -NH-CO-NH-	-O-	4-CH_3-	380.448	381.5	2.255
52.	3-4 -CH_2-CO-NH-	-O-	4-CH_3-	379.46	380.5	2.296
53.	3-4 -N=CH-NH-	-O-	4-CH_3-	364.449	365.5	1.841
54.	3-4 -O-CH_2-CO-NH-	-O-	4-CH_3-	395.459	396.5	2.419
55.	3-4 -NH-N=CH-	-O-	4-CH_3-	364.449	365.5	2.466
56.	3-4 -CH=N-NH-	-O-	4-CH_3-	364.449	365.5	2.418
57.	3-4 -S-C(SH)=N-	-O-	4-CH_3-	413.554	414.4	2.74
58.	3-4 -CH=C(CH_3)-NH-	-O-	4-CH_3-	377.488	378.5	2.702
59.	3-4 -NH-C(CH_3)=N-	-O-	4-CH_3-	378.476	380.5	1.946
60.	3-4 -CH_2-CH_2-CO-NH-	-O-	4-CH_3-	393.487	394.5	2.438
61.	3-4 -NH-CS-NH-	-O-	4-CH_3-	396.509	397.5	2.327
62.	3-4 -O-CO-NH-	-CH_2-	4-CH_3-	379.46	380.5	2.574
63.	3-4 -NH-CO-O-	-CH_2-	4-CH_3-	379.46	380.5	2.544
64.	3-4 -NH-CO-NH-	-CH_2-	4-CH_3-	378.476	379.5	2.433
65.	3-4 -CH_2-CO-NH-	-CH_2-	4-CH_3-	377.488	378.5	2.486
66.	3-4 -O-CH_2-CO-NH-	-CH_2-	4-CH_3-	393.487	394.5	2.592
67.	3-4 -NH-N=CH-	-CH_2-	4-CH_3-	362.477	363.5	2.645
68.	3-4 -CH=N-NH-	-CH_2-	4-CH_3-	362.477	363.5	2.618
69.	3-4 -CH=CH-NH-	-CH_2-	4-CH_3-	361.489	362.5	2.735
70.	3-4 -S-C(SH)=N-	-CH_2-	4-CH_3-	411.582	412.5	2.919
71.	3-4 -CH=C(CH_3)-NH-	-CH_2-	4-CH_3-	375.516	376.5	2.885
72.	3-4 -NH-C(CH_3)=N-	-CH_2-	4-CH_3-	376.504	377.4	2.100
73.	3-4 -CH_2-CH_2-CO-NH-	-CH_2-	4-CH_3-	391.515	392.5	2.612

74.	3-4 -NH-CS-NH-	$-CH_2-$	4-CH_3-	394.537	395.5	2.500
75.	3-4 -S-CO-NH-	$-CH_2-$	4-CH_3-	395.521	396.5	2.733
76.	3-4 -N=CH-NH-	CH_3-N<	4-Cl-	397.91	398.5	1.296
77.	3-4 -O-CH_2-CO-NH-	CH_3-N<	4-Cl-	428.92	429.5	1.896
78.	3-4 -S-C(SH)=N-	CH_3-N<	4-Cl-	447.015	447.5	2.285
79.	3-4 -NH-C(CH_3)=N-	CH_3-N<	4-Cl-	411.937	412.4	1.455
80.	3-4 -CH_2-CH_2-CO-NH-	CH_3-N<	4-Cl-	426.948	427.4	1.937
81.	3-4 -CH_2-CO-NH-	-O-	4-Cl-	399.878	400.4	2.43
82.	3-4 -O-CO-NH-	CH_3-N<	4-Cl-	414.893	415.5	1.827
83.	3-4 -CH=N-NH-	CH_3-N<	4-Cl-	397.91	398.5	1.853
84.	3-4 -NH-N=CH-	CH_3-N<	4-Cl-	397.91	398.5	1.932
85.	3-4 -CH=CH-NH-	CH_3-N<	4-Cl-	396.922	397.5	1.862
86.	3-4 -CH=C(CH_3)-NH-	CH_3-N<	4-Cl-	410.949	411.4	2.130
87.	3-4 -S-CO-NH-	CH_3-N<	4-Cl-	430.954	431.4	2.072
88.	3-4 -O-CO-NH-	$-CH_2-CH_2-$	4-F-	397.45	398.3	2.558
89.	3-4 -NH-CO-O-	$-CH_2-CH_2-$	4-F-	397.45	398.3	2.525
90.	3-4 -CH_2-CO-NH-	$-CH_2-CH_2-$	4-F-	395.478	396.2	2.481
91.	3-4 -N=CH-NH-	$-CH_2-CH_2-$	4-F-	380.467	381.2	1.988
92.	3-4 -O-CH_2-CO-NH-	$-CH_2-CH_2-$	4-F-	411.477	412.2	2.585
93.	3-4 -NH-N=CH-	$-CH_2-CH_2-$	4-F-	380.467	381.2	2.623
94.	3-4 -CH=N-NH-	$-CH_2-CH_2-$	4-F-	380.467	381.2	2.601
95.	3-4 -CH=CH-NH-	$-CH_2-CH_2-$	4-F-	379.479	380.2	2.696
96.	3-4 -S-C(SH)=N-	$-CH_2-CH_2-$	4-F-	429.572	430.4	2.881
97.	3-4 -CH=C(CH_3)-NH-	$-CH_2-CH_2-$	4-F-	393.506	394.2	2.851
98.	3-4 -NH-C(CH_3)=N-	$-CH_2-CH_2-$	4-F-	394.494	395.2	2.085
99.	3-4 -CH_2-CH_2-CO-NH-	$-CH_2-CH_2-$	4-F-	409.505	410.2	2.602
100.	3-4 -NH-CS-NH-	$-CH_2-CH_2-$	4-F-	412.527	413.2	2.475
101.	3-4 -S-CO-NH-	$-CH_2-CH_2-$	4-F-	413.511	414.3	2.716
102.	3-4 -O-CO-NH-	CH_3-N<	4-CH_3-	394.475	395.2	1.467
103.	3-4 -NH-CO-O-	CH_3-N<	4-CH_3-	394.475	395.2	1.48
104	3-4 -NH-CO-NH-	CH_3-N<	4-CH_3-	393.491	394.2	1.423

105.	3-4 -CH_2-CO-NH-	CH_3-N<	4-CH_3-	392.503	393.3	1.444
106.	3-4 -N=CH-NH-	CH_3-N<	4-CH_3-	377.492	378.2	0.966
107.	3-4 -O-CH_2-CO-NH-	CH_3-N<	4-CH_3-	408.502	409.3	1.544
108.	3-4 -CH=CH-NH-	CH_3-N<	4-CH_3-	376.504	377.2	1.453
109.	3-4 -S-C(SH)=N-	CH_3-N<	4-CH_3-	426.597	427.3	1.896
110.	3-4 -CH_2-CH_2-CO-NH-	CH_3-N<	4-CH_3-	406.53	407.3	1.574
111.	3-4 -NH-CS-NH-	CH_3-N<	4-CH_3-	409.552	410.3	1.455
112.	3-4 -S-CO-NH-	CH_3-N<	4-CH_3-	410.536	410.3	1.682
113.	3-4 -CH=C(CH_3)-NH-	CH_3-N<	4-Br-	455.4	456.2	2.211
114.	3-4 -NH-C(CH_3)=N-	CH_3-N<	4-Br-	456.388	457.2	1.522
115.	3-4 -CH_2-CH_2-CO-NH-	CH_3-N<	4-Br-	471.399	472.8	2.001
116.	3-4 -S-CO-NH-	CH_3-N<	4-Br-	475.405	476.2	2.159
117.	3-4 -CH=C(CH_3)-NH-	CH_3-N<	4-CH_3-	390.531	391.3	1.708
118.	3-4 -CH=N-NH-	CH_3-N<	4-CH_3-	377.492	378.3	1.495
119.	3-4 -NH-N=CH-	CH_3-N<	4-CH_3-	377.492	378.3	1.572
120.	3-4 -O-CO-NH-	CH_3-N<	4-Br-	459.344	460.2	1.913
121.	3-4 -CH_2-CO-NH-	CH_3-N<	4-Br-	457.372	458.2	1.839
122.	3-4 -N=CH-NH-	CH_3-N<	4-Br-	442.361	443.2	1.39
123.	3-4 -O-CH_2-CO-NH-	CH_3-N<	4-Br-	473.371	474.2	1.986
124.	3-4 -NH-N=CH-	CH_3-N<	4-Br-	442.361	443.2	2.023
125.	3-4 -CH=N-NH-	CH_3-N<	4-Br-	442.361	443.2	1.949
126.	3-4 -CH=CH-NH-	CH_3-N<	4-Br-	441.373	442.2	1.953
127.	3-4 -S-C(SH)=N-	CH_3-N<	4-Br-	491.466	492.2	2.371
128.	3-4 -NH-CS-NH-	CH_3-N<	4-Br-	474.421	475.2	1.897
129.	3-4 -NH-C(CH_3)=N-	CH_3-N<	4-CH_3-	391.519	392.3	1.151
130.	3-4 -NH-CO-O-	CH_3-N<	4-Br-	459.344	460.2	1.908

Example 123

Preparation of pharmaceutical compositions:

a) Tablets:

0.01-50 % of active ingredient 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 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 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 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 (polyacrilic 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 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 mould in cooled forms.

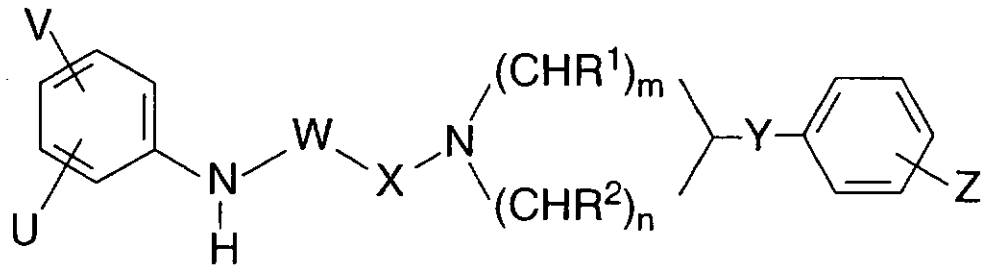
f) Lyophilized powder ampoule compositions:

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

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 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 carboxylic acid amide derivatives of formula (I)



(I)

- wherein

both of $-(CHR^1)_m-$ and $-(CHR^2)_n-$ are $-CH_2-CH_2-$ groups,

the neighboring V and U groups form together and with one or more identical or different additional hetero atom and -CH= and/or $-CH_2-$ groups an optionally substituted 4-7 membered homo- or heterocyclic ring, preferably morpholine, pyrrole, pyrrolidine, oxo- or thioxo-pyrrolidine, pyrazole, pyrazolidine, imidazole, imidazolidine, oxo- or thioxo-imidazole or imidazolidine, 1,4-oxazine, oxazole, oxazolidine, oxo- or thioxo-oxazolidine, or 3-oxo-1,4-oxazine ring,

X is –CO- group,

W is -CO-, $-CH_2-$ or -CH(-alkyl)- group - wherein alkyl is a C_1-C_4 alkyl group,

Y is oxygen atom, as well as C_1-C_4 alkylene, C_2-C_4 alkynylene, cycloalkylene, aminocarbonyl, -NH-, -N(alkyl)- , $-CH_2O-$, -CH(OH)-, $-OCH_2-$ group, - wherein alkyl is a C_1-C_4 alkyl group -

Z is hydrogen or halogen atom, nitro, amino, C_1-C_4 alkyl, C_1-C_4 alkoxy, cyano, trifluoromethyl, hydroxyl or carboxyl group,

and optical antipodes or racemates and/or pharmaceutically acceptable salts thereof formed with acids and bases.

2. Compounds of claim 1, where both of $-(CHR^1)_m-$ and $-(CHR^2)_n-$ are $-CH_2-CH_2-$ groups, X means -CO- group, and W means $-CH_2-$ group, and V, U, Y and Z have the meanings as defined for formula (I).

3. Compounds of claim 1, where both of $-(CHR^1)_m-$ and $-(CHR^2)_n-$ are $-CH_2-CH_2-$ groups, both of X and W mean -CO- groups, and V, U, Y and Z have the meanings as defined for formula (I).

4. One compound of the following group of carboxylic acid amide derivatives belonging to the scope of claim 1

2-[4-(4-fluoro-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-acetamide,
2-[4-(4-fluoro-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide,
2-[4-(4-fluoro-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)-acetamide,
2-(4-benzyl-piperidin-1-yl)-2-oxo-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-acetamide,
2-(4-benzyl-piperidin-1-yl)-2-oxo-N-(2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)-acetamide,
2-(4-benzyl-piperidin-1-yl)-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide,
5-{2-[4-(4-fluoro-benzyl)-piperidin-1-yl]-2-oxo-ethylamino}-1,3-dihydro-benzoimidazol-2-one,
6-{2-[4-(4-fluoro-benzyl)-piperidin-1-yl]-2-oxo-ethylamino}-3H-benzoxazol-2-one,
2-[4-(4-methylbenzyl)-piperidin-1-yl]-2-oxo-N-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-acetamide,
2-[4-[4-methyl-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-acetamide,
2-[4-(4-chloro-phenoxy)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)-acetamide,
2-[4-(4-chloro-phenoxy)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide,
2-[4-(4-chloro-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide,
2-[4-(4-chloro-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)-acetamide,
2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-2-(4-p-tolyloxy-piperidin-1-yl)-acetamide,
2-oxo-N-(2-oxo-2,3-dihydro-1H-benzimidazol-6-yl)-2-(4-p-tolyloxy-piperidin-1-yl)-acetamide,
2-[4-(4-chloro-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-acetamide,
6-[2-(4-benzyl-piperidin-1-yl)-2-oxo-ethylamino]-3H-benzoxazol-2-one,
2-(4-benzyl-piperidin-1-yl)-N-(2-mercapto-3H-benzimidazol-5-yl)-2-oxo-acetamide,
2-(4-benzyl-piperidin-1-yl)-2-oxo-N-(2-oxo-2,3-dihydro-benzothiazol-6-yl)-acetamide,
2-[4-(4-fluoro-benzyl)-piperidin-1-yl]-N-(2-mercapto-3H-benzimidazol-5-yl)-2-oxo-acetamide,

2-[4-(4-fluoro-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzothiazol-6-yl)-acetamide,

2-oxo-N-(2-oxo-2,3-dihydro-benzothiazol-6-yl)-2-(4-p-tolyloxy-piperidin-1-yl)-acetamide,

N-(2-mercapto-3H-benzimidazol-5-yl)-2-(4-p-tolyloxy-piperidin-1-yl)-2-oxo-acetamide,

2-[4-(4-methyl-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl]-acetamide,

2-[4-[4-methoxy-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide,

2-[4-[3-methoxy-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide,

2-[4-[3-methyl-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide,

2-[4-(4-cyano-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide,

2-[4-[3-fluoro-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide,

2-[4-(2,4-difluoro-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide,

6-{2-[4-(4-methyl-benzyl)-piperidin-1-yl]-2-oxo-ethylamino}-3H-benzoxazol-2-one,

2-[4-(3,4-difluoro-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide,

2-[4-(4-methyl-benzyl)-piperidin-1-yl)-2-oxo-N-(2-oxo-1,2,3,4-tetrahidro-quinolin-6-yl-acetamide,

2-[4-(4-methyl-benzyl)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzothiazol-6-yl)-acetamide,

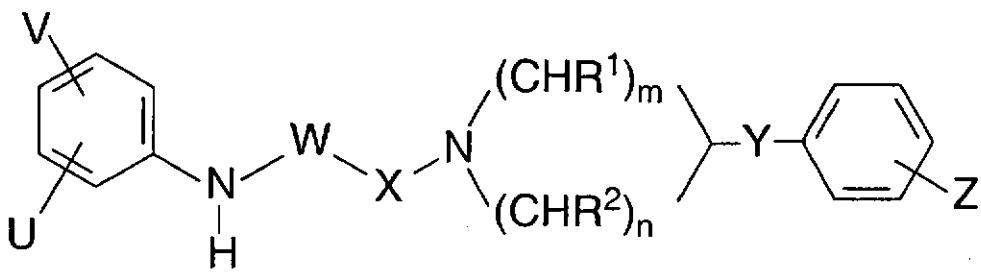
2-[4-(4-chloro-phenoxy)-piperidin-1-yl]-2-oxo-N-(2-oxo-2,3-dihydro-benzothiazol-6-yl)-acetamide,

2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-2-(4-p-tolyloxy-piperidin-1-yl)-acetamide,

and/or the racemates, optical antipodes thereof and/or pharmaceutically acceptable salts of it formed with acids or bases.

5. Pharmaceutical compositions having an NR2B subtype specific NMDA antagonist effect, **characterized by** comprising a biologically effective dose of a carboxylic acid amide derivative of formula (I) – wherein the meaning of R^1, R^2, V, U, W, X, Y, Z , m and n are as defined in claim 1 – and/or the racemates, optical antipodes thereof and/or pharmaceutically acceptable salts of it formed with acids or bases as active ingredient and carriers, filling materials and the like usually applied in pharmaceuticals.

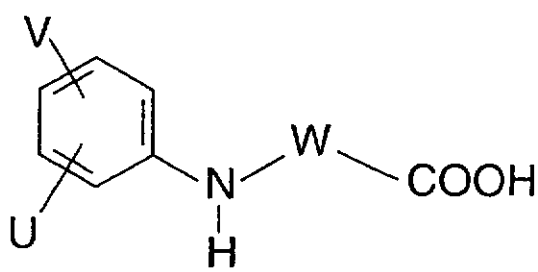
6. Process for the synthesis of carboxylic acid amide derivatives of formula (I),



(I)

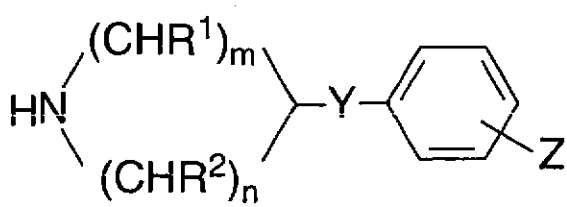
– wherein the meaning of R^1, R^2, V, U, W, X, Y, Z , m and n are as defined in claim 1 – and/or the racemates, optical antipodes thereof and/or pharmaceutically acceptable salts of it formed with acids or bases as active ingredient, **characerized by**

a.) reacting a carboxylic acid of formula (II)



(II)

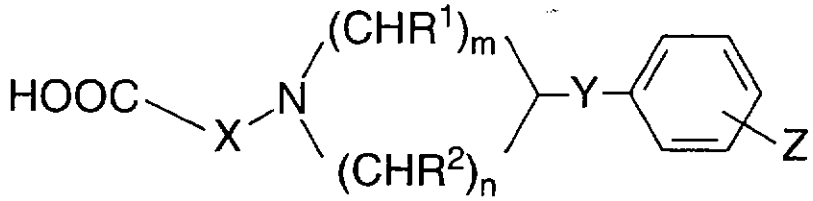
- wherein the meaning of U, V and W are as given for the formula of (I) - or a reactive derivative of it with an amine of formula (III)



(III)

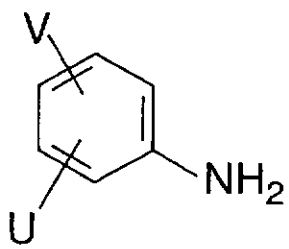
- wherein the meaning of R^1, R^2, Y, Z, n and m are as given before for the formula of (I) - , or

b.) for producing of compounds of formula (I) having -CO- group in place of W - wherein the meaning of R^1, R^2, Y, Z, U, V, X, n and m are as given before for the formula of (I) – reacting a carboxylic acid of formula (IV)



(IV)

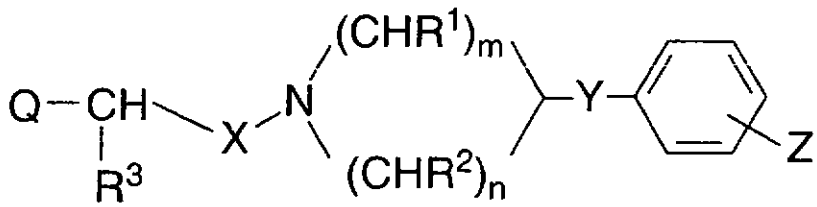
- wherein the meaning of X, R^1, R^2, Y, Z, n and m are as described above for the formula of (I) - or a reactive derivative of it with an amine of formula (V)



(V)

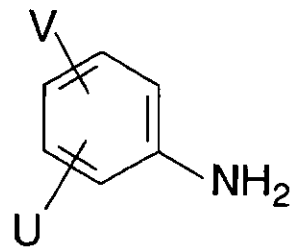
- wherein the meaning of U and V are as given before for the formula of (I) -, or

c.) for producing of compounds of formula (I) having $-CH_2-$ or -CH(-alkyl)- group in place of W - wherein alkyl is a C_1-C_4 alkyl group and the meaning of R^1, R^2, Y, Z, U, V, X, n and m are as given before for the formula of (I) – reacting a halogene derivative of a compound of formula (VII)



(VII)

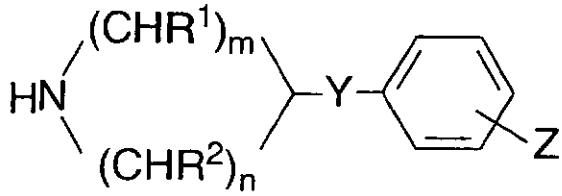
- wherein the meaning of Q is halogen atom, R^3 is hydrogen atom or a C_1-C_4 alkyl group and X, R^1, R^2, Y, Z, n and m are as described above for the formula of (I) - with an amine of formula (V)



(V)

- wherein the meaning of U and V are as given before for the formula of (I) -, or

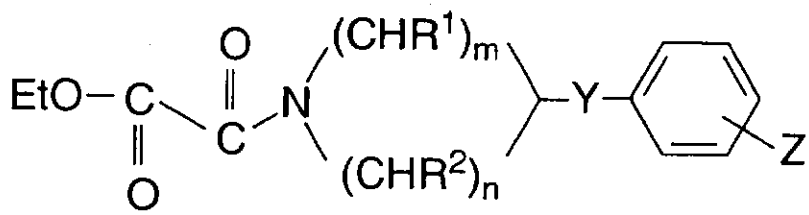
d.) reacting a secondary amine of formula (III)



(III)

- where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I) - with ethyl oxalylchloride in the presence of solid-supported base in dichloromethane,

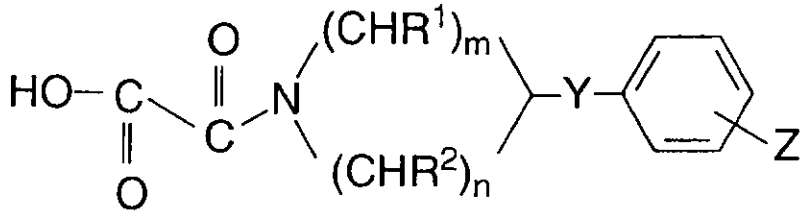
saponifying the obtained ester compound of formula (VIII)



(VIII)

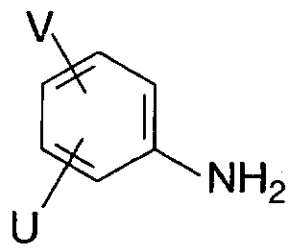
- where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I) - with a strongly basic ion exchange resin in ethanol and

reacting the obtained oxalamid acid of formula (IX)



(IX)

where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I) with an amide of formula (V)



(V)

- wherein the meaning of U and V are as given before for the formula of (I) - in dichloromethan/dimethylformamide mixture in the presence of 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide,

and transforming the obtained compounds of formula (I) - where R^1, R^2, Y, Z, U, V, X, W, n and m are as defined above - in given case into another compound of formula (I) by introducing further substituents and/or modifying and/or removing the existing ones, and/or forming salts with acids and/or liberating the carboxylic acid amide derivative of formula (I) from the obtained acid addition salts by treatment with a base and/or transforming the free carboxylic acid amide derivative of formula (I) into salts by treatment with a base and/or resolving it into their optical antipodes.

7. Process as claimed in claim **6**, **characterized by** forming the reactive derivative of carboxylic acids of formula (II) and (IV) - wherein U, V, W, or X, R^1, R^2, Y, Z, n and m are as given for formula (I), respectively - by using of O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate.

8. Process for manufacturing pharmaceutical compositions having NR2B selective NMDA receptor antagonist effect, **characterized by** mixing a carboxylic acid amide derivative of formula (I) – wherein the meaning of R^1, R^2, V, U, W, X, Y, Z , m and n are

as defined in claim 1 – and/or the racemates, optical antipodes thereof and/or pharmaceutically acceptable salts of it formed with acids or bases with carriers, filling materials and the like usually applied in pharmaceuticals.

9. Use of effective amount/amounts of a carboxylic acid amide derivative of formula (I) – wherein the meaning of R^1, R^2, V, U, W, X, Y, Z, m and n are as defined in claim 1 – and/or the racemates, optical antipodes thereof and/or pharmaceutically acceptable salts of it formed with acids or bases as such or combined with carriers, filling materials and the like usually applied in pharmaceuticals, in the preparation of a medicament for the treatment and alleviation of symptoms of the following diseases of mammals – including human – traumatic injury of brain or spinal cord, human immunodeficiency virus (HIV) related neuronal injury, amyotrophic lateral sclerosis, tolerance and/or dependence to opioid treatment of pain, withdrawal syndromes of e.g. alcohol, opioids or cocaine, ischemic CNS disorders, chronic neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, pain and chronic pain states, such as neuropathic pain or cancer related pain, epilepsy, anxiety, depression, migraine, psychosis, muscular spasm, dementia of various origin, hypoglycemia, degenerative disorders of the retina, glaucoma, asthma, tinnitus, aminoglycoside antibiotic-induced hearing loss.