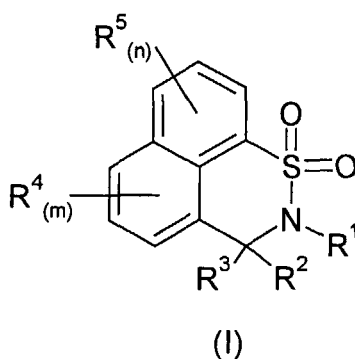


NAPHTHOTHIAZINE POSITIVE ALLOSTERIC AMPA RECEPTOR MODULATORS (PAARM)

5 The present invention relates to new positive allosteric AMPA receptor modulators, processes for preparing them and their use as pharmaceutical compositions.

As compounds which are structurally similar to the compounds according to the invention, WO 9967242 describes carbapenem derivatives with an antibacterial
 10 activity, wherein naphtho[1,8-de]-2,3-dihydro-1,1-dioxide-1,2-thiazine is used as a synthesis component.

The compounds according to the invention are compounds of general formula (I)



wherein

20 R^1 denotes a group selected from among hydrogen, a C_1 - C_6 -alkyl group optionally substituted by one or more halogen atoms, $-SO_2H$, $-SO_2$ - C_1 - C_6 -alkyl, $-SO$ - C_1 - C_6 -alkyl, $-CO$ - C_1 - C_6 -alkyl, $-O$, phenyl- C_1 - C_4 -alkyl, $-C_1$ - C_4 -alkyl- NR^6R^7 and $-C_1$ - C_4 -alkyl- O - C_1 - C_4 -alkyl, and C_3 - C_6 -cycloalkyl,
 R^2 , R^3 , which may be identical or different, denote a group selected from
 25 among hydrogen, a C_1 - C_6 -alkyl group optionally substituted by one or more halogen atoms, halogen, $-NO_2$, $-SO_2H$, $-SO_2$ - C_1 - C_6 -alkyl, $-SO$ - C_1 - C_6 -alkyl, $-CO$ - C_1 - C_6 -alkyl, $-OH$, $-O$ - C_1 - C_6 -alkyl, $-S$ - C_1 - C_6 -alkyl, $-C_1$ - C_4 -alkyl- NR^6R^7 and $-C_1$ - C_4 -alkyl- O - C_1 - C_4 -alkyl and C_3 - C_6 -cycloalkyl, or
 R^1 and R^2 together denote a C_4 - C_6 -alkylene bridge,

R^6 , R^7 , which may be identical or different, denote hydrogen, C_1 - C_4 -alkyl or $-CO$ - C_1 - C_4 -alkyl,

R^8 , R^9 , which may be identical or different, denote hydrogen or C_1 - C_4 -alkyl,

R^4 , which may be identical or different, denotes a group selected from among

5 a C_1 - C_6 -alkyl group optionally substituted by one or more halogen atoms, phenyl- C_1 - C_4 -alkyl, halogen, $-CN$, $-NO_2$, $-SO_2H$, $-SO_3H$, $-SO_2$ - C_1 - C_6 -alkyl, $-SO$ - C_1 - C_6 -alkyl, $-SO_2$ - NR^6R^7 , $-COOH$, $-CO$ - C_1 - C_6 -alkyl, $-O$ - CO - C_1 - C_4 -alkyl, $-CO$ - O - C_1 - C_4 -alkyl, $-O$ - CO - O - C_1 - C_4 -alkyl, $-CO$ - NR^6R^7 , $-OH$, $-O$ - C_1 - C_6 -alkyl, $-S$ - C_1 - C_6 -alkyl, $-NR^6R^7$ and an aryl group optionally mono or polysubstituted by halogen
10 atoms, $-NO_2$, $-SO_2H$ or C_1 - C_4 -alkyl,

R^5 , which may be identical or different, denotes a group selected from among a C_1 - C_6 -alkyl group optionally substituted by one or more halogen atoms,

phenyl- C_1 - C_4 -alkyl, halogen, $-CN$, $-NO_2$, $-SO_2H$, $-SO_3H$, $-SO_2$ - C_1 - C_6 -alkyl, $-SO$ - C_1 - C_6 -alkyl, $-SO_2$ - NR^6R^7 , $-COOH$, $-CO$ - C_1 - C_6 -alkyl, $-O$ - CO - C_1 - C_4 -alkyl, $-CO$ - O - C_1 - C_4 -alkyl, $-O$ - CO - O - C_1 - C_4 -alkyl, $-CO$ - NR^6R^7 , $-OH$, $-O$ - C_1 - C_6 -alkyl, $-S$ - C_1 - C_6 -alkyl, $-NR^6R^7$ and an aryl group optionally mono or polysubstituted by halogen
15 atoms, $-NO_2$, $-SO_2H$ or C_1 - C_4 -alkyl, and

n , m which may be identical or different represent 0, 1, 2 or 3,

with the proviso that naphtho[1,8-de]-2,3-dihydro-1,1-dioxide-1,2-thiazine is

20 excluded,

optionally in the form of their various enantiomers and diastereomers, and the pharmacologically acceptable salts thereof.

Preferred compounds are the compounds of general formula (I), wherein

25 R^1 denotes a group selected from among hydrogen, a C_1 - C_6 -alkyl group optionally substituted by one or more halogen atoms, $-SO_2H$, $-SO_2$ - C_1 - C_6 -alkyl, $-SO$ - C_1 - C_6 -alkyl, $-CO$ - C_1 - C_6 -alkyl, $-O$, $-C_1$ - C_4 -alkyl- NR^7R^8 and $-C_1$ - C_4 -alkyl- O - C_1 - C_4 -alkyl, benzyl,

30 R^2 , R^3 , which may be identical or different, denote a group selected from among hydrogen, a C_1 - C_6 -alkyl group optionally substituted by one or more halogen atoms, halogen, $-NO_2$, $-SO_2H$, $-SO_2$ - C_1 - C_6 -alkyl, $-SO$ - C_1 - C_6 -alkyl, $-CO$ -

C₁-C₆-alkyl, -OH, -O-C₁-C₆-alkyl, -S-C₁-C₆-alkyl, -C₁-C₄-alkyl-NR⁶R⁷ and -C₁-C₄-alkyl-O-C₁-C₄-alkyl, or

R¹ and R² together denote a C₄-C₆-alkylene bridge,

R⁶, R⁷, which may be identical or different, denote hydrogen, C₁-C₄-alkyl or -CO-C₁-C₂-alkyl,

and

R⁴, which may be identical or different, denotes a group selected from among a C₁-C₆-alkyl group optionally substituted by one or more halogen atoms,

halogen, -CN, -NO₂, -SO₂H, -SO₃H, -COOH, -CO-C₁-C₆-alkyl, -O-CO-C₁-C₄-alkyl, -CO-O-C₁-C₄-alkyl, -O-CO-O-C₁-C₄-alkyl, -CO-NR⁶R⁷, -OH, -O-C₁-C₆-alkyl, -S-C₁-C₆-alkyl and -NR⁶R⁷,

R⁵, which may be identical or different, denotes a group selected from among a C₁-C₆-alkyl group optionally substituted by one or more halogen atoms,

halogen, -CN, -NO₂, -SO₂H, -SO₃H, -COOH, -CO-C₁-C₆-alkyl, -O-CO-C₁-C₄-alkyl, -CO-O-C₁-C₄-alkyl, -O-CO-O-C₁-C₄-alkyl, -CO-NR⁶R⁷, -OH, -O-C₁-C₆-alkyl, -S-C₁-C₆-alkyl and -NR⁶R⁷, and

n, m which may be identical or different represent 0, 1 or 2,

optionally in the form of the various enantiomers and diastereomers thereof, as well as the pharmacologically acceptable salts thereof.

Particularly preferred are compounds of general formula (I), wherein

R¹ denotes hydrogen, C₁-C₄-alkyl or benzyl,

R², R³ which may be identical or different, denote hydrogen or C₁-C₄-alkyl, or

R¹ and R² together denote a butylene bridge, and

R⁴, which may be identical or different, denotes a group selected from among a C₁-C₆-alkyl group optionally substituted by one or more halogen atoms,

halogen, -CN, -NO₂, -COOH, -CO-C₁-C₆-alkyl, -O-CO-C₁-C₄-alkyl, -CO-O-C₁-C₄-alkyl, -O-CO-O-C₁-C₄-alkyl, -CO-NR⁶R⁷, -OH, -O-C₁-C₆-alkyl, -S-C₁-C₆-alkyl and -NR⁶R⁷,

R⁵, which may be identical or different, denotes a group selected from among a C₁-C₆-alkyl group optionally substituted by one or more halogen atoms,

halogen, -CN, -NO₂, -COOH, -CO-C₁-C₆-alkyl, -O-CO-C₁-C₄-alkyl, -CO-O-C₁-C₄-alkyl, -O-CO-O-C₁-C₄-alkyl, -CO-NR⁶R⁷, -OH, -O-C₁-C₆-alkyl, -S-C₁-C₆-alkyl and -NR⁶R⁷, and

n, m which may be identical or different represent 0, 1 or 2,

5

optionally in the form of the various enantiomers and diastereomers thereof, as well as the pharmacologically acceptable salts thereof.

Also particularly preferred are compounds of general formula (I), wherein

10

R¹, R², R³, which may be identical or different, denote hydrogen or C₁-C₄-alkyl, R⁴, which may be identical or different, denotes a group selected from among a C₁-C₆-alkyl group optionally substituted by one or more halogen atoms, halogen, -NO₂, -O-CO-C₁-C₄-alkyl, -O-CO-O-C₁-C₄-alkyl, -O-C₁-C₆-alkyl, and -NR⁶R⁷,

15

R⁵, which may be identical or different, denotes a group selected from among a C₁-C₆-alkyl group optionally substituted by one or more halogen atoms, halogen, -NO₂, -O-CO-C₁-C₄-alkyl, -O-CO-O-C₁-C₄-alkyl, -O-C₁-C₆-alkyl, and -NR⁶R⁷, and

n, m which may be identical or different represent 0, 1 or 2,

20

optionally in the form of the various enantiomers and diastereomers thereof, as well as the pharmacologically acceptable salts thereof.

Of particular importance according to the invention are the compounds of general formula (I), wherein R¹ denotes methyl, ethyl, i-propyl, n-butyl or benzyl,

25

optionally in the form of the various enantiomers and diastereomers thereof, as well as the pharmacologically acceptable salts thereof.

30

Particularly preferred are compounds of general formula (I) wherein

R¹ denotes methyl,

optionally in the form of the pharmacologically acceptable salts thereof.

Also particularly preferred are compounds of general formula (I), wherein

R¹ denotes methyl,

R², R³ denote hydrogen,

5 R⁴, R⁵, which may be identical or different, denote halogen, preferably fluorine, chlorine, bromine, most preferably fluorine or chlorine, and

n, m which may be identical or different represent 0, 1 or 2, preferably 0 or 1, optionally in the form of the pharmacologically acceptable salts thereof.

10

The alkyl groups used, unless otherwise stated, are branched and unbranched alkyl groups having 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms. Examples include: methyl, ethyl, propyl, butyl, pentyl and hexyl. The groups methyl, ethyl, propyl or butyl may optionally also be referred to by the abbreviations Me, Et, Pr or

15 Bu. Unless otherwise stated, the definitions propyl, butyl, pentyl and hexyl also include all possible isomeric forms of the groups in question. Thus, for example, propyl includes n-propyl and iso-propyl, butyl includes iso-butyl, sec. butyl and tert.-butyl, etc.

20 In the abovementioned alkyl groups, one or more hydrogen atoms may optionally be substituted by the halogen atoms fluorine, chlorine, bromine or iodine. The substituents fluorine and chlorine are preferred. The substituent fluorine is particularly preferred. If desired, all the hydrogen atoms of the alkyl group may be replaced.

25

The alkyl group mentioned in the group phenyl-C₁-C₄-alkyl may be in branched or unbranched form. Unless otherwise stated benzyl and phenylethyl are preferred phenyl-C₁-C₄-alkyl groups. Benzyl is particularly preferred.

30 The alkyl groups mentioned in the groups -SO₂-C₁-C₆-alkyl, -SO-C₁-C₆-alkyl, -CO-C₁-C₆-alkyl, -CO-C₁-C₄-alkyl, -C₁-C₄-alkyl-NR⁶R⁷, -C₁-C₄-alkyl-O-C₁-C₄-alkyl, -O-C₁-C₆-alkyl, -S-C₁-C₆-alkyl, -O-CO-C₁-C₄-alkyl, -CO-O-C₁-C₄-alkyl or -O-CO-O-C₁-C₄-

alkyl may be in branched or unbranched form with 1 to 6 carbon atoms, preferably with 1 to 4 carbon atoms, particularly preferably with 1 to 3 carbon atoms, most preferably with 1 to 2 carbon atoms.

- 5 The C₄-C₆-alkylene bridge may, unless otherwise stated, be branched and unbranched alkylene groups having 4 to 6 carbon atoms, for example n-butylene, 1-methylpropylene, 2-methylpropylene, 1.1-dimethylethylene, 1.2-dimethylethylene etc. n-Butylene bridges are particularly preferred.
- 10 The aryl group is an aromatic ring system having 6 to 10 carbon atoms, preferably phenyl.

In the abovementioned aryl groups, one or more hydrogen atoms may optionally be substituted by halogen atoms, -NO₂, -SO₂H or -C₁-C₄-alkyl, preferably fluorine, chlorine, -NO₂, ethyl or methyl, most preferably fluorine or methyl.

15

The term C₃-C₆-cycloalkyl denotes saturated cyclic hydrocarbon groups having 3 - 6 carbon atoms, for example cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

- The term halogen, unless otherwise stated, refers to fluorine, chlorine, bromine and
20 iodine, preferably fluorine, chlorine and bromine, most preferably fluorine and chlorine, most preferably fluorine.

- As already mentioned, the compounds of formula (I) or the various enantiomers and diastereomers thereof may be converted into the salts thereof, particularly, for
25 pharmaceutical use, into the physiologically and pharmacologically acceptable salts thereof. These salts may on the one hand take the form of physiologically and pharmacologically acceptable acid addition salts of the compounds of formula (I) with inorganic or organic acids. On the other hand, the compound of formula (I) where R¹ is hydrogen may be converted by reaction with inorganic bases into
30 physiologically and pharmacologically acceptable salts with alkali or alkaline earth metal cations as counter-ions. The acid addition salts may be prepared, for example, using hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid,

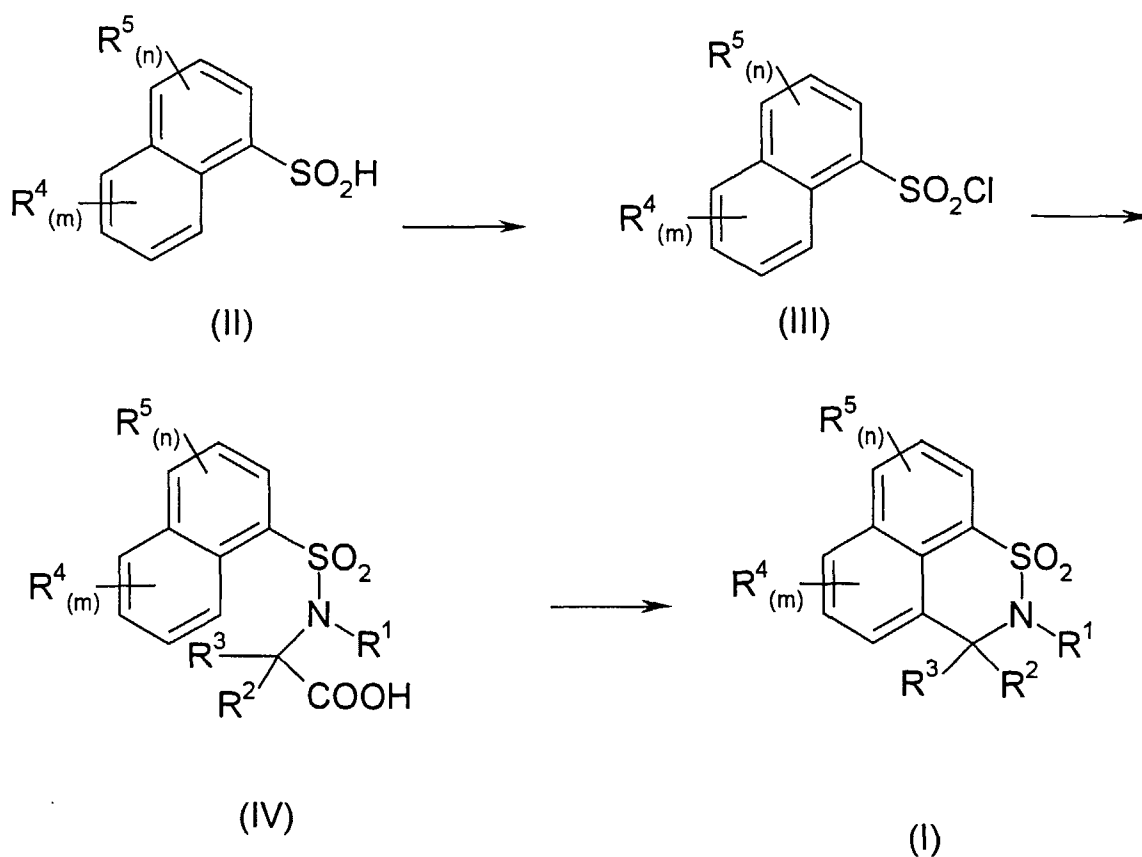
methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid. It is also possible to use mixtures of the above acids. For preparing the alkali and alkaline earth metal salts of the compound of formula (I) wherein R^1 denotes hydrogen, it is preferable to use the alkali and alkaline earth metal hydroxides and hydrides, the hydroxides and hydrides of the alkali metals, especially sodium and potassium, being preferred, while sodium and potassium hydroxide are particularly preferred.

The compounds according to the invention may be prepared in a manner known *per se*. The following general methods of synthesis 1 and 2 shown in Diagrams 1 and 2 below are meant to illustrate the invention without restricting it to their content.

Method 1

Diagram 1

15



Starting from a compound of formula (II) a compound of formula (III) is prepared by sulphonation and subsequent chlorination. The compound of formula (IV) obtained after condensation with aminoacetic acid derivatives is cyclised by adding
5 polyphosphoric acid to the target compound (I).

The general preparation of the compounds according to the invention in accordance with Diagram 1 is described in detail hereinafter.

10 Sulphonation of the naphthalenes (II):

About 10 mmol of the naphthalene derivative (II) are taken up in 2 - 100 ml, preferably 3 - 80 ml, most preferably about 4 ml, of acetic anhydride and 10 - 100 mmol, preferably 11 - 80 mmol, particularly preferably 11 mmol or conc. sulphuric acid are added at 0 - 50°C, preferably 5 - 20°C, particularly preferably about 18 °C.

15 After 2 - 16 h, preferably about 5 h, stirring at 20 - 100°C, preferably about 25 C°, the mixture is poured onto a saturated NaCl solution. The crystals formed are isolated.

Methylene chloride, diisopropylether, ethyl acetate, trichloromethane, toluene, benzene or 1,4-dioxin may be used instead of acetic acid anhydride, while fuming
20 sulphuric acid, sulphur trioxide, chlorine sulphates or combinations thereof may be used as an alternative to conc. sulphuric acid.

Synthesis of the naphthalene-1-sulphonic acid chlorides (III):

About 10 mmol of the naphthalene-1-sulphonic acids are combined successively
25 with 10 - 500 mmol, preferably about 90 mmol, of phosphorus oxytrichloride and 8 - 50 mmol, preferably about 10 mmol, of phosphorus pentachloride and heated for 2 - 16 h, preferably about 5 h, at 20 - 100°C, preferably by refluxing. Then the reaction mixture is evaporated down and combined with water. After extraction with organic diluent the combined organic extracts are dried and freed from solvent. The crude
30 product obtained is used in the subsequent steps without being purified.

Instead of the phosphorus oxytrichloride/phosphorus pentachloride mixture, thionyl chloride, phosphorus pentachloride, a phosphoric acid/chlorine mixture or phosgene

may be used. The reaction may alternatively be carried out in the diluents ethyl acetate, water, acetonitrile, N,N-dimethylacetamide, sulpholane, DMF, hexane or dichloroethane.

5 Synthesis of the naphthalene-1-sulphonyl-amino-acetic acids :

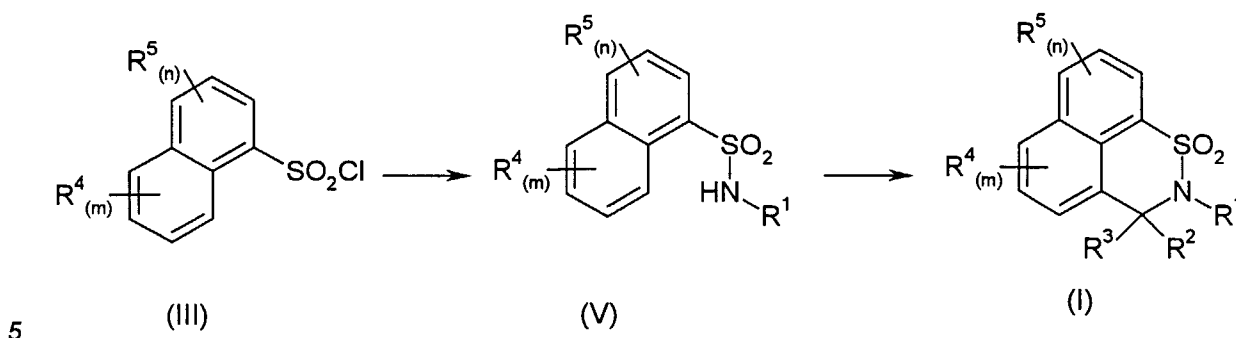
About 10 mmol of the chlorosulphonyl-naphthalenes, 10 - 100 mmol, preferably 11 - 30 mmol, most preferably about 12 mmol, of aminoacetic acid and 10 - 100 mmol, preferably 11 - 30 mmol, most preferably about 12 mmol, of sodium hydroxide are dissolved in water and toluene. The reaction mixture is stirred for 2 - 16 h at 0 -
10 110°C, preferably at about 65°C, then the phases are separated. The aqueous phase is acidified and extracted. The combined organic extracts are dried and evaporated down. Purification may be carried out by chromatography.
Triethylamine, potassium carbonate, sodium hydrogen carbonate or sodium hydride may be used instead of sodium hydroxide, while tetrahydrofuran, diethylether,
15 dichloromethane, trichloromethane, dioxin, acetone, benzene, ethanol, methanol, ethyl acetate or acetonitrile may be used instead of toluene.

Cyclisation of the naphthalene-1-sulphonyl-amino-acetic acids (IV):

About 10 mmol of the naphthalene-1-sulphonyl-amino-acetic acids are combined
20 with 10 - 200 g, preferably about 40 g, of polyphosphoric acid and stirred for 2 - 16 h, preferably about 5 h, at 20 - 110°C, preferably 75 - 95°C, most preferably at about 80°C . Then the reaction mixture is poured onto water and extracted. The combined organic extracts are dried and evaporated down. The residue is purified.

Method 2

Diagram 2



The compounds of formula (III) obtained as intermediate compounds in Method 1 are reacted with primary amines to obtain the compounds of formula (V) and then cyclised by the addition of a compound of formula $R^2R^3C=O$ in the presence of strong acid to obtain the target compounds (I).

10 In order to prepare the compounds of formula (I) wherein R¹ and R² represent hydrogen, paraformaldehyde, trioxane or formalin may be used and methanesulphonic acid, trifluoroacetic acid, sulphuric acid, phosphoric acid or polyphosphoric acid may be used as strong acids.

15 The general preparation of the compounds according to the invention in accordance with Diagram 2 is described in detail hereinafter.

Synthesis of the naphthalene-sulphonamides (V):

About 10 mmol of the chlorosulphonyl-naphthalenes (III) are combined with an
20 alcoholic solution of the primary amine (10 - 1000 mmol in 5 - 200 ml, for example
200 mmol in 50 ml ethanol) and then heated to 0 - 100 °C for 2 - 16 h, preferably
about 5 h, preferably by refluxing. Then the reaction mixture is evaporated down
and purified.

Instead of the alcoholic solvent it is also possible to use toluene, benzene,
25 trichloromethane, dichloromethane, diethylether, tetrahydrofuran, water, acetonitrile,
acetic anhydride, acetone, pyridine, dimethylsulphoxide, dimethylformamide, dioxin
or hexane.

Cyclisation of the naphthalene-1-sulphonamides (V) to form the target compounds (I):

About 10 mmol of the naphthalene-1-sulphonamides are added to 0 - 100 ml,
5 preferably 20 - 80 ml, most preferably about 40 ml of methanesulphonic acid and
combined with a solution of 3 - 50 mmol, preferably 4 - 30 mmol, most preferably 5
mmol of trioxane in 0 - 100 ml, preferably about 12 ml, of trifluoroacetic acid. The
reaction mixture is stirred for 2 - 16 h, preferably 5 h, at 20 - 100 °C, preferably 30 -
80 °C, most preferably about 35°C and then poured onto ice water. After extraction
10 and drying of the combined organic extracts the solution is evaporated down. The
crude product is purified.

Instead of trioxane it is possible to use paraformaldehyde or formalin, while instead
of trifluoroacetic acid it is possible to use boron trifluoride*diethylether, acetic acid,
polyphosphoric acid, phosphoric acid or sulphuric acid. Acetic anhydride or
15 dichloromethane may be used as possible diluents.

The new compounds of general formula (I) may be synthesised analogously to the
following Examples of synthesis. These Examples are, however, intended solely as
examples of procedure to illustrate the invention further without restricting it to the
20 subject matter thereof.

Synthesis of 2-methyl-2,3-dihydro-naphtho[1,8-de][1,3]thiazine- 1,1-dioxide
(Example 1):

2.21 g of N-methyl-1-naphthalenesulphonic acid amide are dissolved in 25 ml of
25 methanesulphonic acid at 35°C and combined with a solution of 0.30 g of trioxane in
8 ml of trifluoroacetic acid. After 2 h stirring at ambient temperature The reaction
mixture is poured onto 300 ml of ice water. The solid formed is separated off by
filtration, washed with 100 ml of water and dried overnight. After crystallisation from
methylcyclohexane the product is isolated as a white solid. Yield: 2.20 g. M.p.:
30 136°C.

Synthesis of 6-chloro-2-methyl-2,3-dihydro-naphtho[1,8-de][1,3]thiazine-1,1-dioxide (Example 2):

0.45 g of 5-chloro-naphthalene-1-sulphonic acid-N-methylamide are dissolved in 6.8
5 ml of methanesulphonic acid at 35°C and combined with a solution of 0.07 g of
trioxane in 2 ml of trifluoroacetic acid. After 2 h stirring at 35°C The reaction mixture
is poured onto 100 ml of ice water and the aqueous phase is extracted with ethyl
acetate. The organic extracts collected are dried with sodium sulphate, evaporated
down in vacuo and then purified by chromatography. Yield: 0.41 g. M.p.: 150°C.

10

**Synthesis of 2,3-dihydro-naphtho[1,8-de][1,3]thiazine- 1,1-dioxide
(Example 3):**

Naphthalene-1-sulphonic acid tert-butylamide:

15 8 ml of tert. butylamine are placed in 50 ml of chloroform, cooled to 0° C and 5.75 g
of 1-naphthalenic acid chloride in 45 ml of chloroform are added dropwise. Then the
mixture is stirred for 24 h at ambient temperature. After concentration by evaporation
in vacuo the residue obtained is dissolved in dichloromethane and washed with 2 N
hydrochloric acid. The organic extracts collected are dried with sodium sulphate and
20 evaporated down in vacuo. Yield: 5.48 g.

2-tert-butyl-1,1-dioxo-1,2-dihydro-1λ⁶-naphtho[1,8-de][1,3]thiazin-3-one:

4.36 g of naphthalene-1-sulphonic acid tert-butylamide are placed in 80 ml
tetrahydrofuran, cooled to -10° C and 29 ml of N-butyl lithium (1.6 molar solution in
25 hexane) are cautiously added dropwise. The mixture is first stirred for 0.5 h at -10°
C, then for 3 h at ambient temperature. Then it is cooled to -5° C and within 0.25 h
CO₂ obtained from dry ice is piped in. The reaction mixture is stirred for 2.5 h at
ambient temperature, then combined with water. The solution is poured onto 4 N
hydrochloric acid and extracted with ethyl acetate. The organic extracts collected are
30 dried with sodium sulphate and after evaporation in vacuo purified by
chromatography. Yield: 0.42 g.

2-tert-butyl-2,3-dihydro-naphtho[1,8-de][1,3]thiazine-1,1-dioxide:

0.17 g of 2-*tert*-butyl-1,1-dioxo-1,2-dihydro-1 λ^6 -naphtho[1,8-de][1,3]thiazin-3-one are suspended in 2 ml tetrahydrofuran at ambient temperature, 1.17 ml of borane-tetrahydrofuran complex (1 molar Solution) are added. Then the mixture is refluxed with stirring for 100 h, with a total of a further 8.2 ml of 1M borane-tetrahydrofuran complex solution being added in several batches. The reaction mixture is combined with 2 ml of 2 N hydrochloric acid and with 2 ml of methanol, then refluxed for 12 h with stirring. 2 ml of ammonia are added and any crystals formed are filtered off. The filtrate is extracted with ethyl acetate, the organic extracts collected are dried with sodium sulphate. After evaporation in vacuo the residue obtained is purified by chromatography. Yield: 0.06 g.

2,3-Dihydro-naphtho[1,8-de][1,3]thiazine-1,1-dioxide:

0.06 g of 2-*tert*-butyl-2,3-dihydro-naphtho[1,8-de][1,3]thiazin-1,1-dioxide are dissolved in 1 ml of dichloromethane and 0.02 ml of trifluoroacetic acid are added. Then the mixture is stirred for a total of 22 h at reflux temperature and for 96 h at ambient temperature, while during this period a total of 0.07 ml of trifluoroacetic acid are added. The reaction mixture is evaporated down in vacuo and purified by chromatography. Yield: 0.034 g. M.p.: 206°-207° C.

Synthesis of [2-(1,1-dioxo-1H-3H-1 λ^6 -naphtho[1,8-de]thiazine-2-yl)ethyl]dimethylamine (Example 4):

0.028 g of sodium hydride are suspended in 0.5 ml of dimethylformamide and 0.073 g of 2,3-dihydro-naphtho[1,8-de][1,3]thiazine-1,1-dioxide in 1 ml of dimethylformamide are added. Then 0.053 g of diethylaminoethyl chloride-hydrochloride are added batchwise. The reaction mixture is stirred for 18 h at ambient temperature and then poured onto ice water. The mixture is extracted with dichloromethane and the organic extracts collected are dried with sodium sulphate. After evaporation in vacuo the residue obtained is purified by chromatography. Yield: 0.035 g. M.p.: 97°-98°C.

Synthesis of N-(2-methyl-1,1-dioxo-2,3-dihydro-1H-1 λ^6 -naphtho[1,8-de][1,3]thiazin-6-yl)-acetamide: (Example 5):

5-acetylamino-naphthalene-1-sulphonylchloride:

5 1.40 g of 5-acetylamino-naphthalene-1-sulphonic acid and 2.23 g of phosphorus pentachloride are combined and stirred for 4 h at 60° C. Then the solution is poured onto ice water and extracted with dichloromethane. The organic extracts collected are dried with sodium sulphate and evaporated down in vacuo. Yield: 1.10 g.

10

N-(5-methylsulphamoyl-naphthalene-1-yl)-acetamide:

1.10 g of 5-acetylamino-naphthalene-1-sulphonyl chloride are dissolved in 8 ml of ethanol and 8 ml of methylamine solution in ethanol are added dropwise. Then the resulting mixture is stirred at reflux temperature for 3.5 h and the solvent is distilled
15 off in vacuo. The residue is purified by chromatography. Yield: 0.50 g.

N-(2-methyl-1,1-dioxo-2,3-dihydro-1H-1 λ^6 -naphtho[1,8-de][1,3]thiazin-6-yl)-acetamide:

0.25 g of N-(5-methylsulphamoyl-naphthalene-1-yl)-acetamide are dissolved in 3.4
20 ml of methanesulphonic acid at 35° C and combined with a solution of 0.027 g of trioxane in 1 ml of trifluoroacetic acid. After 6 h stirring at 35° C the reaction mixture is poured onto ice water and the aqueous phase extracted with ethyl acetate. The organic extracts collected are dried with sodium sulphate, evaporated down in vacuo and purified by chromatography. Yield: 0.136 g. M.p.: 189°-190° C.

25

Synthesis of 2-(1,1-Dioxo-1H,3H-1 λ^6 -naphtho[1,8-de][1,3]thiazin-2-yl)-acetamide: (Example 6):

8-tert-butylsulphamoyl-naphthalene-1-carboxylic acid:

30 4.36 g of naphthalene-1-sulphonic acid *tert*-butylamide are placed in 80 ml tetrahydrofuran, cooled to -10° C and 29 ml of N-butyl lithium (1.6 molar solution in hexane) are cautiously added dropwise. The mixture is stirred first for 0.5 h at -10°C, then for 3 h at ambient temperature. It is then cooled to -5°C and CO₂ obtained from dry ice is piped in within 0.25 h. The reaction mixture is stirred for 2.5
35 h at ambient temperature and then combined with water. The solution is poured onto 4 N hydrochloric acid and extracted with ethyl acetate. The organic extracts collected are dried with sodium sulphate and after evaporation in vacuo purified by chromatography. Yield: 1.19 g.

1,1-Dioxo-1,1-dihydro-1 λ^6 -naphtho[1,8-de][1,3]thiazin-3-one:

0.25 g of polyphosphoric acid are taken and 0.15 g of 8-*tert*-butylsulphamoyl-naphthalene-1-carboxylic acid is added. The mixture is stirred for 4 h at 150°C. Then
5 the reaction mixture is poured onto ice water and the aqueous phase is extracted with ethyl acetate. The organic extracts collected are dried with sodium sulphate and evaporated down in vacuo. Yield: 0.07 g.

2,3-Dihydro-naphtho[1,8-de][1,3]thiazine-1,1-dioxide:

10 0.07 g of 1,1-dioxo-1,1-dihydro-1 λ^6 -naphtho[1,8-de][1,3]thiazin-3-one are dissolved in 2 ml of tetrahydrofuran and then 1.2 ml of 1 molar borane-tetrahydrofuran complex solution is carefully added dropwise. The mixture is stirred for 18 h at reflux temperature. The reaction mixture is combined with 1.5 ml of 2 N hydrochloric acid and 2 ml of methanol, then stirred for 2 h at reflux temperature. 2 ml of ammonia are
15 added and any crystals formed are filtered off. The filtrate is extracted with ethyl acetate, the organic extracts collected are dried with sodium sulphate and evaporated down in vacuo. Yield: 0.06 g.

2-(1,1-Dioxo-1H,3H-1 λ^6 -naphtho[1,8-de][1,3]thiazin-2-yl)-acetamide:

20 0.011 g of sodium hydride are suspended in 0.5 ml of dimethylformamide, and 0.06 g of 2,3-dihydro-naphtho[1,8-de][1,3]thiazine-1,1-dioxide in 1 ml of dimethylformamide are added. The mixture is stirred for 1 h at ambient temperature and then 0.042 g of 2-bromoacetamide are added batchwise. Then the mixture is stirred for 18 h at ambient temperature. The reaction mixture is poured onto ice water and extracted
25 with dichloromethane. The organic extracts collected are dried with sodium sulphate and after evaporation in vacuo purified by chromatography. Yield: 0.043 g. M.p.: 195°-196° C.

30 **Synthesis of 7-hydroxy-2-methyl-2,3-dihydro-naphtho[1,8-de][1,3]thiazine-1,1-dioxide (Example 7):**

0.6 g of 7-methoxy-2-methyl-2,3-dihydro-naphtho[1,8-de][1,3]thiazine-1,1-dioxide are dissolved in 23 ml dichloromethane and the solution is cooled to -78° C. 2.3 ml of boron tribromide (1 molar solution in dichloromethane) are added dropwise. Then
35 the mixture is stirred for 24 h at ambient temperature. After evaporation in vacuo the residue is purified by chromatography. Yield: 0.36 g. M.p.: 245°-246° C.

Synthesis of methyl 2-methyl-1,1-dioxo-2,3-dihydro-1H-1 λ ⁶-naphtho[1,8-de][1,3]thiazin-7-yl ester carboxylate (Example 8):

- 0.11 g of 7-hydroxy-2-methyl-2,3-dihydro-naphtho[1,8-de][1,3]thiazine-1,1-dioxide
5 and 0.061 ml triethylamine are placed in 2 ml toluene and cooled to 0°C. 0.037 ml of
methyl chloroformate are added dropwise. Then the mixture is stirred for 5 h at
ambient temperature. The suspension is then poured onto ice water and extracted
with ethyl acetate. The organic extracts collected are dried with sodium sulphate
and, after evaporation in vacuo, purified by chromatography.
10 Yield: 0.065g. M.p.: 161°-162°C.

The following compounds of formula IA are obtained, *inter alia*, analogously to the procedure described hereinbefore:

5

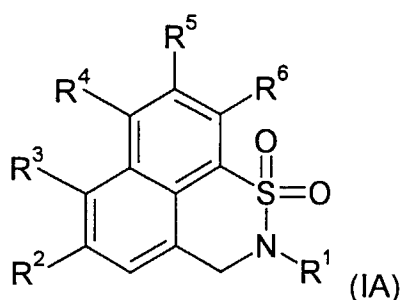


Table 1

Example	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Mp.[°C]
9	CH ₃	H	H	H	H	Br	226-227
10	CH ₃	NO ₂	H	H	H	H	264-265
11	CH ₃	H	H	OCH ₃	H	H	174-175
12	CH ₃	H	H	F	H	H	129-130
13	CH ₃	H	H	Br	H	H	163-164
14	CH ₃	H	H	CH ₃	H	H	142-143
15	CH ₃	H	H	I	H	H	192-193
16	CH ₃	H	I	H	H	H	160-161
17	CH ₃	H	NO ₂	H	H	H	169-170
18	CH ₃	H	OH	H	H	H	160-161
19	CH ₃	N(CH ₃) ₂	H	H	H	H	
20	CH ₃	H	H	H	H	N(CH ₃) ₂	
21	CH ₃	i-Pr	H	H	iso-Pr	H	
22	CH ₃	H	OCOMe	H	H	H	
23	CH ₃	H	F	H	H	H	

10

It has been found that the compounds of general formula (I) are characterised by their wide range of applications in the therapeutic field. Particular mention should be

made of those applications in which the positive modulation of AMPA receptors plays a part.

The effect of the compounds according to the invention as AMPA receptor modulators was measured electrophysiologically on cells which express functional
5 AMPA receptors. Investigations were carried out to see whether the test substances have a positive allosteric influence on the agonist-induced current.

The test was carried out at concentrations of between 0.3 μmol and 300 μmol .

10 Table 2: Intensification of the agonist-induced current (+ good, ++ very good activity)

Example	Activity
1	+
2	++

The new compounds can also be used to treat illnesses or conditions in which neuronal networks which require AMPA receptors in order to function are damaged
15 or limited in their function.

The compounds of general formula (I) can thus be used in dementias, in neurodegenerative or psychotic illnesses and in neurodegenerative disorders and cerebral ischaemias of various origins, preferably in schizophrenia or learning and memory disorders.

20

The following are also included: epilepsy, hypoglycaemia, hypoxia, anoxia, cerebral trauma, brain oedema, amyotrophic lateral sclerosis, Huntington's Disease, Alzheimer's disease, sexual dysfunction, disorders of sensory/motor function, memory formation, hyperkinetic behavioural changes (particularly in children),
25 hypotension, cardiac infarct, cerebral pressure (increased intracranial pressure), ischaemic and haemorrhagic stroke, global cerebral ischaemia on stoppage of the heart, acute and chronic neuropathic pain, diabetic polyneuropathy, tinnitus, perinatal asphyxia, psychosis, Parkinson's disease and depression, and related anxiety states.

The new compounds may also be given in conjunction with other active substances, such as those used for the same indications, or for example with neuroleptics, nootropics, psychostimulants, etc. They may be administered topically, orally, 5 transdermally, nasally, parenterally or by inhalation. Moreover, the compounds of general formula I or the salts thereof may also be combined with active substances of other kinds.

The compounds of general formula (I) may be given on their own or in conjunction 10 with other active substances according to the invention, and possibly also in conjunction with other pharmacologically active substances. Suitable preparations include for example tablets, capsules, suppositories, solutions, - particularly solutions for injection (s.c., i.v., i.m.) and infusion - elixirs, emulsions or dispersible powders. The content of the pharmaceutically active compound(s) should be in the 15 range from 0.1 to 90 wt.-%, preferably 0.5 to 50 wt.-% of the composition as a whole, i.e. in amounts which are sufficient to achieve the dosage range specified below. Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such 20 as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

Coated tablets may be prepared accordingly by coating cores produced analogously 25 to the tablets with substances normally used for tablet coatings, for example collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number of layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

30

Syrups or elixirs containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharine,

cyclamate, glycerol or sugar and a flavour enhancer, e.g. a flavouring such as vanilline or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or
5 preservatives such as p-hydroxybenzoates.

Solutions for injection and infusion are prepared in the usual way, e.g. with the addition of isotonic agents, preservatives such as p-hydroxybenzoates, or stabilisers such as alkali metal salts of ethylenediamine tetraacetic acid, optionally using
10 emulsifiers and/or dispersants, whilst if water is used as the diluent, for example, organic solvents may optionally be used as solvating agents or dissolving aids, and transferred into injection vials or ampoules or infusion bottles.

Capsules containing one or more active substances or combinations of active
15 substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules.
Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof.
Excipients which may be used include, for example, water, pharmaceutically
20 acceptable organic solvents such as paraffins (e.g. petroleum fractions), vegetable oils (e.g. groundnut or sesame oil), mono- or polyfunctional alcohols (e.g. ethanol or glycerol), carriers such as e.g. natural mineral powders (e.g. kaolins, clays, talc, chalk), synthetic mineral powders (e.g. highly dispersed silicic acid and silicates), sugars (e.g. cane sugar, lactose and glucose) emulsifiers (e.g. lignin, spent sulphite
25 liquors, methylcellulose, starch and polyvinylpyrrolidone) and lubricants (e.g. magnesium stearate, talc, stearic acid and sodium lauryl sulphate).

The preparations are administered by the usual methods, preferably by oral or transdermal route, particularly orally. For oral administration the tablets may of
30 course contain, apart from the abovementioned carriers, additives such as sodium citrate, calcium carbonate and dicalcium phosphate together with various additives such as starch, preferably potato starch, gelatine and the like. Moreover, lubricants

such as magnesium stearate, sodium lauryl sulphate and talc may be used at the same time for the tableting process. In the case of aqueous suspensions the active substances may be combined with various flavour enhancers or colourings in addition to the excipients mentioned above.

- 5 For parenteral use, solutions of the active substances with suitable liquid carriers may be used.

The dosage for intravenous use is from 1 - 1000 mg per hour, preferably between 5 and 500 mg per hour.

- 10 However, it may sometimes be necessary to depart from the amounts specified, depending on the body weight, the route of administration, the individual response to the drug, the nature of its formulation and the time or interval over which the drug is administered. Thus, in some cases it may be sufficient to use less than the minimum dose given above, whereas in other cases the upper limit may have to be exceeded.
- 15 When administering large amounts it may be advisable to divide them up into a number of smaller doses spread over the day.

The following examples of formulations illustrate the present invention without restricting its scope:

Examples of Pharmaceutical Formulations

5

A)	<u>Tablets</u>	<u>per Tablet</u>
	active substance	100 mg
	lactose	140 mg
10	maize starch	240 mg
	polyvinylpyrrolidone	15 mg
	magnesium stearate	5 mg
		500 mg

15

The finely-ground active substance, lactose and some of the maize starch are mixed together. The mixture is screened, then moistened with a solution of polyvinylpyrrolidone in water, kneaded, wet-granulated and dried. The granules, the remaining maize starch and the magnesium stearate are screened and mixed
20 together. The mixture is compressed to produce tablets of suitable shape and size.

B)	<u>Tablets</u>	<u>per Tablet</u>
	active substance	80 mg
25	lactose	55 mg
	maize starch	190 mg
	microcrystalline cellulose	35 mg
	polyvinylpyrrolidone	15 mg
	sodium-carboxymethyl starch	23 mg
30	magnesium stearate	2 mg
		400 mg

The finely ground active substance, some of the corn starch, lactose, microcrystalline cellulose and polyvinylpyrrolidone are mixed together, the mixture is screened and worked with the remaining corn starch and water to form a granulate
5 which is dried and screened. The sodiumcarboxymethyl starch and the magnesium stearate are added and mixed in and the mixture is compressed to form tablets of a suitable size.

C) Ampoule solution

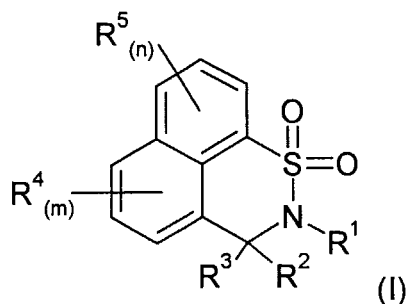
10

active substance	50 mg
sodium chloride	50 mg
aqua for inj.	5 ml

15 The active substance is dissolved in water at its own pH or optionally at pH 5.5 to 6.5 and sodium chloride is added to make it isotonic. The solution obtained is filtered free from pyrogens and the filtrate is transferred under aseptic conditions into ampoules which are then sterilised and sealed by fusion. The ampoules contain 5 mg, 25 mg and 50 mg of active substance.

Patent Claims

1) Compounds of general formula (I)



wherein

R^1 denotes a group selected from among hydrogen, a C_1 - C_6 -alkyl group optionally substituted by one or more halogen atoms, $-SO_2H$, $-SO_2$ - C_1 - C_6 -alkyl, $-SO$ - C_1 - C_6 -alkyl, $-CO$ - C_1 - C_6 -alkyl, $-O$, phenyl- C_1 - C_4 -alkyl, $-C_1$ - C_4 -alkyl- NR^6R^7 and $-C_1$ - C_4 -alkyl- O - C_1 - C_4 -alkyl, and C_3 - C_6 -cycloalkyl,

R^2 , R^3 , which may be identical or different, denote a group selected from among hydrogen, a C_1 - C_6 -alkyl group optionally substituted by one or more halogen atoms, halogen, $-NO_2$, $-SO_2H$, $-SO_2$ - C_1 - C_6 -alkyl, $-SO$ - C_1 - C_6 -alkyl, $-CO$ - C_1 - C_6 -alkyl, $-OH$, $-O$ - C_1 - C_6 -alkyl, $-S$ - C_1 - C_6 -alkyl, $-C_1$ - C_4 -alkyl- NR^6R^7 and $-C_1$ - C_4 -alkyl- O - C_1 - C_4 -alkyl and C_3 - C_6 -cycloalkyl, or

R^1 and R^2 together denote a C_4 - C_6 -alkylene bridge,

R^6 , R^7 , which may be identical or different, denote hydrogen, C_1 - C_4 -alkyl or $-CO$ - C_1 - C_4 -alkyl,

R^4 , which may be identical or different, denotes a group selected from among a C_1 - C_6 -alkyl group optionally substituted by one or more halogen atoms, phenyl- C_1 - C_4 -alkyl, halogen, $-CN$, $-NO_2$, $-SO_2H$, $-SO_3H$, $-SO_2$ - C_1 - C_6 -alkyl, $-SO$ - C_1 - C_6 -alkyl, $-SO_2$ - NR^6R^7 , $-COOH$, $-CO$ - C_1 - C_6 -alkyl, $-O$ - CO - C_1 - C_4 -alkyl, $-CO$ - O - C_1 - C_4 -alkyl, $-O$ - CO - O - C_1 - C_4 -alkyl, $-CO$ - NR^6R^7 , $-OH$, $-O$ - C_1 - C_6 -alkyl, $-S$ - C_1 - C_6 -alkyl, $-NR^6R^7$ and an aryl group optionally mono or polysubstituted by halogen atoms, $-NO_2$, $-SO_2H$ or C_1 - C_4 -alkyl,

R^5 , which may be identical or different, denotes a group selected from among a C_1 - C_6 -alkyl group optionally substituted by one or more halogen atoms, phenyl- C_1 - C_4 -alkyl, halogen, $-CN$, $-NO_2$, $-SO_2H$, $-SO_3H$, $-SO_2$ - C_1 - C_6 -alkyl, $-SO$ -

C₁-C₆-alkyl, -SO₂-NR⁶R⁷, -COOH, -CO-C₁-C₆-alkyl, -O-CO-C₁-C₄-alkyl, -CO-O-C₁-C₄-alkyl, -O-CO-O-C₁-C₄-alkyl, -CO-NR⁶R⁷, -OH, -O-C₁-C₆-alkyl, -S-C₁-C₆-alkyl, -NR⁶R⁷ and an aryl group optionally mono or polysubstituted by halogen atoms, -NO₂, -SO₂H or C₁-C₄-alkyl, and

5 n, m which may be identical or different represent 0, 1, 2 or 3,
with the proviso that naphtho[1,8-de]-2,3-dihydro-1,1-dioxide-1,2-thiazine is excluded,

optionally in the form of the various enantiomers and diastereomers thereof, as
10 well as the pharmacologically acceptable salts thereof.

2) Compounds of general formula (I) according to claim 1, wherein

R¹ denotes a group selected from among hydrogen, a C₁-C₆-alkyl group optionally substituted by one or more halogen atoms, -SO₂H, -SO₂-C₁-C₆-alkyl,
15 -SO-C₁-C₆-alkyl, -CO-C₁-C₆-alkyl, -O, -C₁-C₄-alkyl-NR⁷R⁸ and -C₁-C₄-alkyl-O-C₁-C₄-alkyl, benzyl,

R², R³, which may be identical or different, denote a group selected from among hydrogen, a C₁-C₆-alkyl group optionally substituted by one or more halogen atoms, halogen, -NO₂, -SO₂H, -SO₂-C₁-C₆-alkyl, -SO-C₁-C₆-alkyl, -CO-C₁-C₆-alkyl, -OH, -O-C₁-C₆-alkyl, -S-C₁-C₆-alkyl, -C₁-C₄-alkyl-NR⁶R⁷ and -C₁-C₄-alkyl-O-C₁-C₄-alkyl, or
20

R¹ and R² together denote a C₄-C₆-alkylene bridge,

R⁶, R⁷, which may be identical or different, denote hydrogen, C₁-C₄-alkyl or -CO-C₁-C₂-alkyl,

25 and

R⁴, which may be identical or different, denotes a group selected from among a C₁-C₆-alkyl group optionally substituted by one or more halogen atoms, halogen, -CN, -NO₂, -SO₂H, -SO₃H, -COOH, -CO-C₁-C₆-alkyl, -O-CO-C₁-C₄-alkyl, -CO-O-C₁-C₄-alkyl, -O-CO-O-C₁-C₄-alkyl, -CO-NR⁶R⁷, -OH, -O-C₁-C₆-alkyl, -S-C₁-C₆-alkyl and -NR⁶R⁷,
30

R⁵, which may be identical or different, denotes a group selected from among a C₁-C₆-alkyl group optionally substituted by one or more halogen atoms,

halogen, -CN, -NO₂, -SO₂H, -SO₃H, -COOH, -CO-C₁-C₆-alkyl, -O-CO-C₁-C₄-alkyl, -CO-O-C₁-C₄-alkyl, -O-CO-O-C₁-C₄-alkyl, -CO-NR⁶R⁷, -OH, -O-C₁-C₆-alkyl, -S-C₁-C₆-alkyl and -NR⁶R⁷, and

n, m which may be identical or different represent 0, 1 or 2,

5

optionally in the form of the various enantiomers and diastereomers thereof, as well as the pharmacologically acceptable salts thereof.

3) Compounds of general formula (I) according to claim 1 or 2, wherein

10

R¹ denotes hydrogen, C₁-C₄-alkyl or benzyl,

R², R³ which may be identical or different, denote hydrogen or C₁-C₄-alkyl, or

R¹ and R² together denote a butylene bridge, and

R⁴, which may be identical or different, denotes a group selected from among a C₁-C₆-alkyl group optionally substituted by one or more halogen atoms,

15

halogen, -CN, -NO₂, -COOH, -CO-C₁-C₆-alkyl, -O-CO-C₁-C₄-alkyl, -CO-O-C₁-C₄-alkyl, -O-CO-O-C₁-C₄-alkyl, -CO-NR⁶R⁷, -OH, -O-C₁-C₆-alkyl, -S-C₁-C₆-alkyl and -NR⁶R⁷,

R⁵, which may be identical or different, denotes a group selected from among a C₁-C₆-alkyl group optionally substituted by one or more halogen atoms,

20

halogen, -CN, -NO₂, -COOH, -CO-C₁-C₆-alkyl, -O-CO-C₁-C₄-alkyl, -CO-O-C₁-C₄-alkyl, -O-CO-O-C₁-C₄-alkyl, -CO-NR⁶R⁷, -OH, -O-C₁-C₆-alkyl, -S-C₁-C₆-alkyl and -NR⁶R⁷, and

n, m which may be identical or different represent 0, 1 or 2,

25

optionally in the form of the various enantiomers and diastereomers thereof, as well as the pharmacologically acceptable salts thereof.

4) Compounds of general formula (I) according to claims 1 to 3, wherein

R¹, R², R³, which may be identical or different, denote hydrogen or C₁-C₄-alkyl,

30

R⁴, which may be identical or different, denotes a group selected from among a C₁-C₆-alkyl group optionally substituted by one or more halogen atoms,

halogen, -NO₂, -O-CO-C₁-C₄-alkyl, -O-CO-O-C₁-C₄-alkyl, -O-C₁-C₆-alkyl, and -NR⁶R⁷,

R⁵, which may be identical or different, denotes a group selected from among a C₁-C₆-alkyl group optionally substituted by one or more halogen atoms,

5 halogen, -NO₂, -O-CO-C₁-C₄-alkyl, -O-CO-O-C₁-C₄-alkyl, -O-C₁-C₆-alkyl, and -NR⁶R⁷, and

n, m which may be identical or different represent 0, 1 or 2,

10 optionally in the form of the various enantiomers and diastereomers thereof, as well as the pharmacologically acceptable salts thereof.

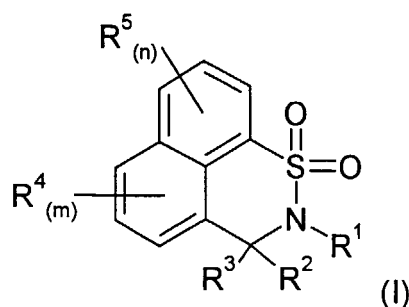
5) Compound of general formula (I) according to one of claims 1 to 4, wherein R¹ denotes methyl, ethyl, i-propyl, n-butyl or benzyl,

15 optionally in the form of the various enantiomers and diastereomers thereof, as well as the pharmacologically acceptable salts thereof.

6) Compounds of general formula (I) according to one of claims 1 to 5, wherein
20 R¹ denotes methyl,
optionally in the form of the pharmacologically acceptable salts thereof.

7) Compounds of general formula (I) according to claim 1, wherein
R¹ denotes methyl,
25 R², R³ denote hydrogen,
R⁴, R⁵ which may be identical or different denote halogen,
and
n, m which may be identical or different represent 0, 1 or 2,
30 optionally in the form of the pharmacologically acceptable salts thereof.

8) Compounds of general formula (I)



wherein

R^1 denotes a group selected from among hydrogen, a C_1 - C_6 -alkyl group optionally substituted by one or more halogen atoms, $-SO_2H$, $-SO_2$ - C_1 - C_6 -alkyl, $-SO$ - C_1 - C_6 -alkyl, $-CO$ - C_1 - C_6 -alkyl, $-O$, phenyl- C_1 - C_4 -alkyl, $-C_1$ - C_4 -alkyl- NR^6R^7 and $-C_1$ - C_4 -alkyl- O - C_1 - C_4 -alkyl, and C_3 - C_6 -cycloalkyl,

R^2 , R^3 , which may be identical or different, denote a group selected from among hydrogen, a C_1 - C_6 -alkyl group optionally substituted by one or more halogen atoms, halogen, $-NO_2$, $-SO_2H$, $-SO_2$ - C_1 - C_6 -alkyl, $-SO$ - C_1 - C_6 -alkyl, $-CO$ - C_1 - C_6 -alkyl, $-OH$, $-O$ - C_1 - C_6 -alkyl, $-S$ - C_1 - C_6 -alkyl, $-C_1$ - C_4 -alkyl- NR^6R^7 and $-C_1$ - C_4 -alkyl- O - C_1 - C_4 -alkyl and C_3 - C_6 -cycloalkyl, or

R^1 and R^2 together denote a C_4 - C_6 -alkylene bridge,

R^6 , R^7 , which may be identical or different, denote hydrogen, C_1 - C_4 -alkyl or $-CO$ - C_1 - C_4 -alkyl,

R^4 , which may be identical or different, denotes a group selected from among a C_1 - C_6 -alkyl group optionally substituted by one or more halogen atoms, phenyl- C_1 - C_4 -alkyl, halogen, $-CN$, $-NO_2$, $-SO_2H$, $-SO_3H$, $-SO_2$ - C_1 - C_6 -alkyl, $-SO$ - C_1 - C_6 -alkyl, $-SO_2$ - NR^6R^7 , $-COOH$, $-CO$ - C_1 - C_6 -alkyl, $-O$ - CO - C_1 - C_4 -alkyl, $-CO$ - O - C_1 - C_4 -alkyl, $-O$ - CO - O - C_1 - C_4 -alkyl, $-CO$ - NR^6R^7 , $-OH$, $-O$ - C_1 - C_6 -alkyl, $-S$ - C_1 - C_6 -alkyl, $-NR^6R^7$ and an aryl group optionally mono or polysubstituted by halogen atoms, $-NO_2$, $-SO_2H$ or C_1 - C_4 -alkyl,

R^5 , which may be identical or different, denotes a group selected from among a C_1 - C_6 -alkyl group optionally substituted by one or more halogen atoms, phenyl- C_1 - C_4 -alkyl, halogen, $-CN$, $-NO_2$, $-SO_2H$, $-SO_3H$, $-SO_2$ - C_1 - C_6 -alkyl, $-SO$ - C_1 - C_6 -alkyl, $-SO_2$ - NR^6R^7 , $-COOH$, $-CO$ - C_1 - C_6 -alkyl, $-O$ - CO - C_1 - C_4 -alkyl, $-CO$ - O - C_1 - C_4 -alkyl, $-O$ - CO - O - C_1 - C_4 -alkyl, $-CO$ - NR^6R^7 , $-OH$, $-O$ - C_1 - C_6 -alkyl, $-S$ - C_1 - C_6 -

alkyl, $-NR^6R^7$ and an aryl group optionally mono or polysubstituted by halogen atoms, $-NO_2$, $-SO_2H$ or C_1-C_4 -alkyl, and

n, m which may be identical or different represent 0, 1, 2 or 3,

5 optionally in the form of their various enantiomers and diastereomers, and the pharmacologically acceptable salts thereof

for use as pharmaceutical compositions.

10 9) Compound of general formula (I) according to claim 8 for use as pharmaceutical compositions with a neuroprotective effect.

10) Use of a compound of general formula (I) according to one of claims 1 to 7 for preparing a pharmaceutical composition for the treatment and/or prevention of
15 neurodegenerative diseases and/or cerebral ischaemia of various origins.

11) Use of a compound of general formula (I) according to one of claims 1 to 7 for preparing a pharmaceutical composition for the treatment of schizophrenia.

20 12) Use of a compound of general formula (I) according to one of claims 1 to 7 for preparing a pharmaceutical composition for the treatment and/or prevention of memory disorders.

25 13) Use of a compound of general formula (I) according to one of claims 1 to 7 for preparing a pharmaceutical composition for the treatment of dementias.

14) Method of treating and/or preventing neurodegenerative diseases and/or cerebral ischaemia, characterised in that a patient is given an effective amount of a compound of formula I according to claims 1 to 7.

- 15) Method of treating and/or preventing memory disorders and/or dementias, characterised in that a patient is given an effective amount of a compound of formula I according to claims 1 to 7.
- 5 16) Pharmaceutical preparations containing as active substance one or more compounds of general formula (I) according to one of claims 1 to 7 or the physiologically acceptable salts thereof optionally combined with conventional excipients and/or carriers.