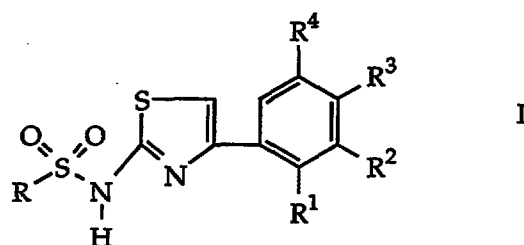


- 5 The invention is concerned with the use of sulphonamide derivatives of the general formula



10 wherein

R signifies lower-alkyl, phenyl, benzyl, naphthyl, pyridyl or thienyl, optionally substituted by one or more lower-alkyl, lower-alkoxy, lower-alkyl-carbonyl-amino, halogen, cycloalkyl, nitro, amino, methylenedioxy, phenoxy or benzyloxy substituents, and the aromatic rings, can, in turn, be substituted by nitro, halogen or amino,

20 R¹-R⁴ signify hydrogen, halogen, hydroxy, lower-alkyl, nitro, cyano, amino, lower-alkoxy, benzyloxy, trifluoromethyl or phenyl, optionally substituted by one or more lower-alkyl, trifluoromethyl, nitro, amino or hydroxy substituents, and wherein R¹ and R² or R² and R³ together can form a benzene ring which optionally can be substituted by halogen, trifluoromethyl, nitro, lower-alkyl or lower-alkoxy,

30 and of their pharmaceutically acceptable salts as kynurenin-3-hydroxylase inhibitors in the control or prevention of neurodegenerative disorders, neurological disorders resulting from an activation of the immune system or psychiatric illnesses and, respectively, for the production of corresponding medicaments.

2-Thiazolyl-sulphonamides have been known for a long time. US 2,611,770 describes, for example, N-(2-thiazolyl)-2-hydroxypyrimidine-5-sulphonamides as active compounds against viral illnesses or illnesses caused by microorganisms.

5

Isoxazolyl-sulphonamides having endothelin-antagonistic activity, inter alia for the treatment of central nervous system disorders, are described in EP 569 193.

10

Patent Specification WO 94/27979 describes sulphonamide derivatives which contain different heterocycles and which have an endothelin-antagonistic activity.

15

A number of specific 2-arylsulphonamido-4-fluoroaryl-thiazoles having antifungicidal activity are set forth in Agr. Biol. Chem., 40 (6), 1129-1135, 1976.

20

Jour. Indian Chem. Soc., Vol. 39, No. 2, 1962 describes, inter alia, a number of specific thiazolyl-sulphonamides having pesticidal activity.

25

In accordance with the invention it has now been found that 2-thiazolyl-sulphonamides of formula I and their salts have a surprisingly high activity as kynurenin-3-hydroxylase inhibitors. Kynurenin-3-hydroxylase inhibitors, alone or in combination with kynurenin or tryptophan, are of therapeutic interest in all disorders and conditions which are associated with a malfunction of glutamatergic neurotransmission and/or which lead to an excessive production of quinolinic acid. Included among these disorders are not only neurodegenerative disorders (Huntington's chorea, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, epilepsy), consequences of stroke and/or cerebral ischaemia, hypoxia, multi-infarct dementia, consequences of cerebral trauma or damage as well as trauma and damage to the spinal cord, neurological disorders resulting from an activation of the immune system (e.g. AIDS-dementia complex, infections such as e.g. viral or bacterial meningitis and cancers with cerebral localization), autoimmune diseases (multiple

35

sclerosis) as well as psychiatric illnesses (schizophrenia, chronic anxiety).

Moreover, it has been found that the compounds have
 5 antibacterial activities, e.g. against *Staphylococcus aureus* and *Streptococcus pyogenes*. This makes these compounds especially interesting, since a two-fold attack in one pharmaceutical application is advantageous for certain types of disease, e.g. in the case of bacterial meningitis or infections which are caused by
 10 the AIDS dementia complex.

Objects of the present invention are the use of compounds of formula I and of pharmaceutically usable salts thereof in the control or prevention of illnesses of the aforementioned kind and,
 15 respectively, for the production of corresponding medicaments, novel compounds of formula I and salts thereof per se and for use as therapeutically active substances, the manufacture of the novel compounds and salts as well as medicaments containing a novel compound of formula I or salt and the production of
 20 corresponding medicaments.

When compounds of general formula I are used in the control or prevention of illnesses of the kind described above, there are preferred those compounds in which R signifies 4-methylphenyl,
 25 4-methoxyphenyl, 4-aminophenyl, 3,4-dimethoxyphenyl or 2-naphthyl and R¹-R⁴ signify hydrogen, fluorine, nitro or trifluoromethyl or R² and R³ together form a benzene ring.

The following are examples of preferred compounds:
 30

4-Methoxy-N-(4-naphthalen-2-yl-thiazol-2-yl)-benzene-sulphonamide,

4-amino-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzene-sulphonamide,

35 4-methyl-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzene-sulphonamide,

3,4-dimethoxy-N-[4-(3-nitro-phenyl)thiazol-2-yl]-benzenesulphonamide,

4-methoxy-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-
benzenesulphonamide,

naphthalene-2-sulphonic acid [4-(3-nitro-phenyl)-thiazol-
2-yl]-amide,

5 N-[4-(2-fluoro-5-trifluoromethyl-phenyl)-thiazol-2-yl]-4-
methyl-benzenesulphonamide,

N-[4-(3-fluoro-5-trifluoromethyl-phenyl)-thiazol-2-yl]-4-
methyl-benzenesulphonamide,

4-methyl-N-[4-(4-nitro-phenyl)-thiazol-2-yl]-benzene-
10 sulphonamide,

4-amino-N-[4-(2-fluoro-5-trifluoromethyl-phenyl)-
thiazol-2-yl]-benzenesulphonamide and

3,4-dimethoxy-N-[4-(2-fluoro-5-trifluoromethyl-phenyl)-
thiazol-2-yl]-benzenesulphonamide.

15

The term "alkyl" used in the present description denotes
straight-chain or branched saturated hydrocarbon groups such as
methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, s-butyl,
t-butyl and the like. The term "lower" denotes in this connection
20 1-7, preferably 1-4, carbon atoms.

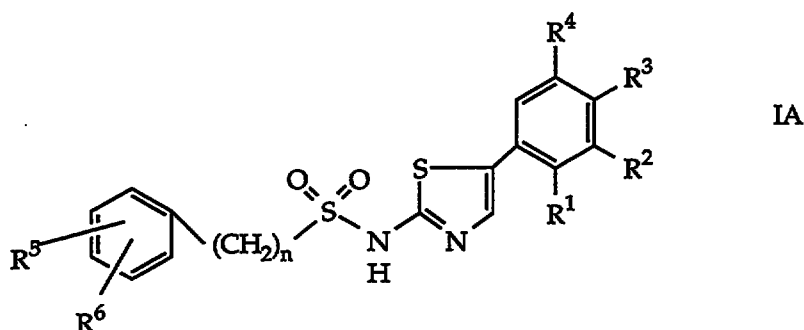
The term "alkoxy" denotes an alkyl group in the sense of the
foregoing definition bonded via an oxygen atom.

25 The term "leaving group" used in the present description
embraces preferably metal-alkyl groups such as tributyltin or
metal halogen groups such as e.g. the zinc chloride group or a
boric acid group.

30 "Halogen" signifies fluorine, chlorine, bromine or iodine.

Novel compounds falling under general formula I, i.e.
compounds of general formulae IA-IE, and their salts are also an
object of the invention:

35



wherein

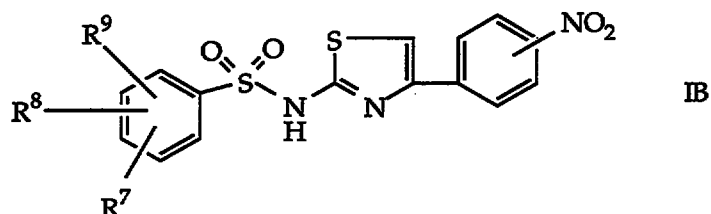
R¹-R⁴ have the aforementioned significances,

R⁵ signifies hydrogen or lower-alkyl,

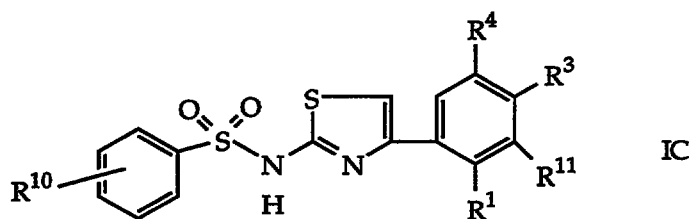
R⁶ signifies hydrogen, lower-alkyl, lower alkoxy, cycloalkyl or benzyl and

n signifies 0 or 1 and

in which R⁵ and R⁶ together can form a methylenedioxy group, and with the proviso that R⁵ and R⁶ can not simultaneously be hydrogen;



wherein R⁷-R⁹ signify hydrogen, halogen, lower-alkoxy or 4-NO₂-phenoxy, with the proviso that at least one of R⁷-R⁹ is halogen;



wherein

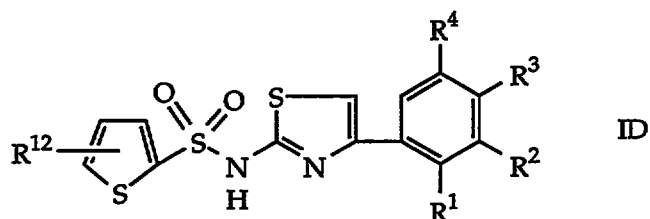
R¹⁰ signifies amino or -NHCOR¹²,

R¹² signifies lower alkyl,

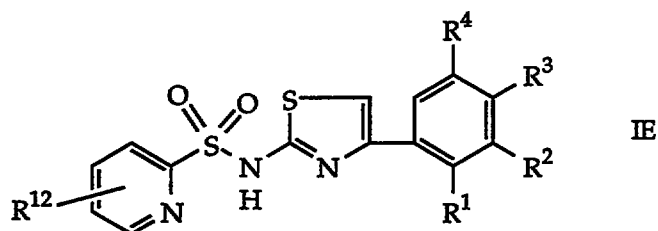
R¹, R³ and R⁴ have the aforementioned significances and

R¹¹ signifies hydrogen, hydroxy, nitro, cyano, amino,

trifluoromethyl, benzyloxy or phenyl, optionally substituted by one or more lower-alkyl, trifluoromethyl, nitro, amino or hydroxy substituents, and R¹¹ and R³ together can form a phenyl ring;



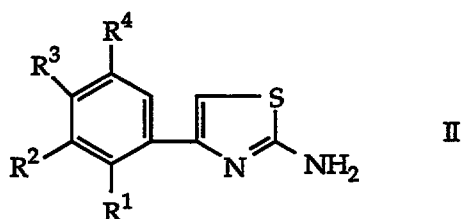
wherein R¹-R⁴ and R¹² have the aforementioned significances;



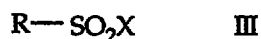
wherein R¹-R⁴ and R¹² have the aforementioned significances.

The novel compounds of formula I can be manufactured in accordance with the invention by

a) reacting a compound of the general formula



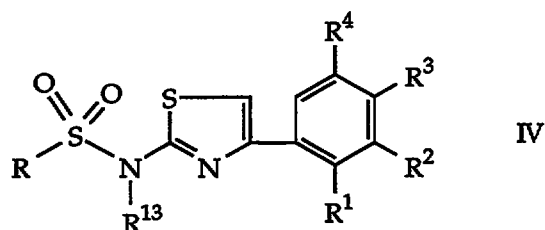
with a suitable sulphonyl halide of the general formula



wherein R and R¹-R⁴ have the aforementioned significances
and X signifies halogen,

or

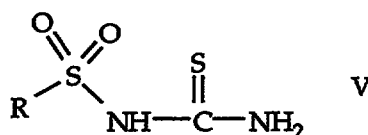
- 5 b) cleaving off the protecting group from a compound of
the general formula



- 10 wherein R¹-R⁴ have the significances given above and R¹³
signifies a sulphonamide protecting group,

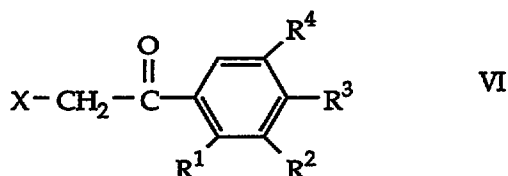
or

- 15 c) reacting a compound of the general formula



wherein R has the significance given above,
with a suitable compound of the general formula

20

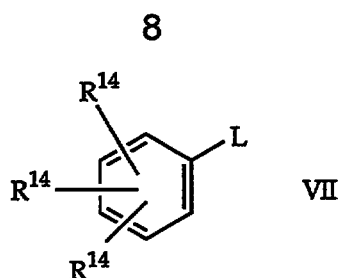


wherein R¹-R⁴ and X have the aforementioned significances,
to give a thiazole derivative of formula I, or

25

- d) reacting a suitable compound of formula IV in which
R² or R³ signifies bromine or iodine and R¹ and/or R⁴ are/is
different from bromine or iodine with a compound of the general
formula

30



wherein L signifies a suitable leaving group and R¹⁴ are the same or different and signify lower-alkyl, lower-alkoxy, trifluoromethyl, nitro, amino or hydroxy,

or

e) hydrolyzing a compound of general formula I in which R signifies phenyl substituted by lower-alkyl-carbonyl-amino and R¹-R⁴ have the aforementioned significances to a compound of general formula I in which R signifies phenyl substituted by amino, and

f) if desired, converting a compound of general formula I into a pharmaceutically acceptable salt.

In accordance with process variant a) a compound of general formula II is treated with a corresponding sulphonyl halide of formula III and stirred for several hours in the presence of pyridine.

The following are especially well suited as sulphonyl halides: p-toluenesulphonyl chloride, p-methoxybenzenesulphonyl chloride, p-Cl-benzenesulphonyl chloride, 3,4-dichlorobenzene-sulphonyl chloride, benzo[1,3]dioxol-5-sulphonyl chloride, 5-isopropyl-pyridine-2-sulphonyl chloride, 3,5-dichloro-4-nitro-phenoxy-benzoyl chloride, naphthalene-2-sulphonyl chloride, 4-cyclohexyl-benzenesulphonyl chloride, 4-isopropyl-benzene-sulphonyl chloride, 4-acetamino-benzenesulphonyl chloride, 3,4-dimethoxy-benzenesulphonyl chloride, 5-tert.-butyl-thiophene-2-sulphonyl chloride, butanesulphonyl chloride and the like.

In accordance with process variant b) a compound of general formula IV is deprotected. Suitable protecting groups and methods for their cleavage will be familiar to any person skilled

in the art, with, of course, preferred protecting groups being those which can be cleaved off by methods involving conditions under which other structural elements in the compounds of formula IV are not affected. All known sulphonamide protecting
5 groups are suitable as the sulphonamide protecting group, with the methoxymethylene group (MOM) being preferred. The cleavage is effected in the acidic range, for example by the addition of hydrochloric acid.

10 Process variant c), in which a compound of formula V and a compound of formula VI react together to form the thiazole ring, represents a further possibility for the manufacture of compounds of formula I. Conveniently, an appropriately substituted sulphonylthiourea compound dissolved in an alcohol, for
15 example ethanol, is treated with an appropriate 2-halo-1-phenyl-1-ethanone compound and the reaction mixture is boiled for a brief period.

According to process variant d) a compound of general
20 formula IV is reacted with a compound of general formula VII. Conveniently, this reaction is effected in the presence of a catalyst, e.g. tetrakis(triphenylphosphine)-palladium and lithium chloride with an aryl metal compound, e.g. phenylboric acid, in the presence of potassium carbonate. Toluene is conveniently used as
25 the solvent. There are obtained compounds of formula I in which R^2 is phenyl optionally substituted by one or more lower-alkyl, lower-alkoxy, trifluoromethyl, nitro, amino or hydroxy substituents.

30 The salt formation in accordance with variant f) of the process in accordance with the invention is effected according to methods which are generally usual and which will be familiar to any person skilled in the art. Basic compounds of formula I can be converted into pharmaceutically acceptable acid addition salts,
35 for example with hydrogen chloride, hydrogen bromide, phosphoric acid, sulphuric acid, citric acid, p-toluenesulphonic acid and the like. Acidic compounds of formula I can form pharmaceutically acceptable salts with suitable bases, for example alkali metal

salts such as sodium or potassium salts or alkaline earth metal salts such as magnesium or calcium salts.

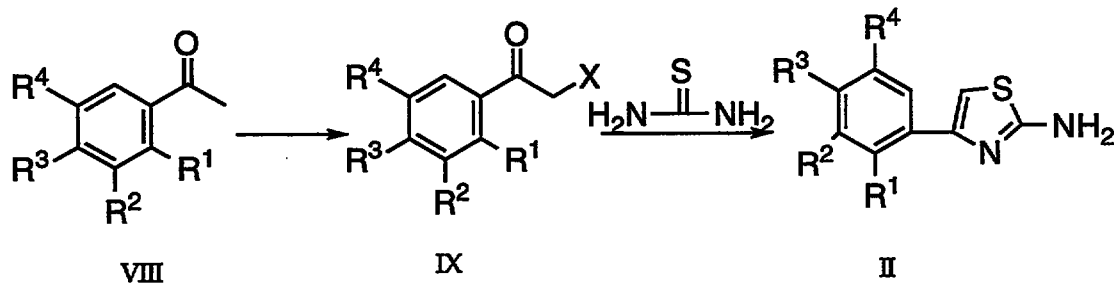
The starting materials of formulae II, III, IV, V, VI and VII
 5 required for the manufacture of the compounds of formula I are known compounds or can be prepared in analogy to known processes. These reactions will be familiar to any person skilled in the art. Furthermore, the preparation of some intermediates is described in Examples 52-65.

10

Scheme 1 hereinafter shows the preparation of compounds of general formula II.

Scheme 1

15



In this scheme, R¹-R⁴ have the aforementioned significances and X signifies halogen.

20

As mentioned earlier, the sulphonamide derivatives of formula I have valuable pharmacological properties and they are accordingly suitable for the control or prevention of illnesses or conditions which are associated with a malfunction of glutam-
 25 atergic neurotransmission and/or which lead to an excessive production of quinolinic acid.

Kynurenic acid and quinolinic acid, two body-specific substances of the tryptophan degradation pathway via kynurenin,
 30 influence the N-methyl-D-aspartate (NMDA) binding sites of the glutamate receptor. Changes in the tissue level of these two substances are associated with neurological disorders and psychiatric illnesses. Quinolinic acid is strongly neurotoxic, while kynurenic acid exhibits neuroprotective activities. The

enzyme kynurenin-3-monooxygenase (kynurenin-3-hydroxylase) is responsible in the tryptophan degradation pathway for the conversion of kynurenin into 3-hydroxykynurenin, a quinolinic acid precursor. Inhibitors of this enzyme on the one hand reduce the formation of the neurotoxin quinolinic acid and on the other hand lead to an increased formation of the neuroprotective-acting kynurenic acid by the inhibition-mediated increased availability of kynurenin.

10 The compounds in accordance with the invention have as kynurenin-3-hydroxylase inhibitors a higher activity than known inhibitors such as m-nitrobenzoylalanine, 3,4-dichloro-benzoylalanine and/or nicotinylalanine. The compounds in accordance with the invention are active in rodents not only after intraperitoneal injection, but also after oral administration.

Determination of kynurenin-3-hydroxylase *in vitro* and *ex vivo*

20 The kynurenin-3-hydroxylase inhibiting activity of the compounds in accordance with the invention can be determined *in vitro* and *ex vivo* using standard methods. The preparations to be tested were examined in the tests described hereinafter, which are based on the methods published by J.B. Erickson, E.M. Flanagan, S. Russo and J.F. Reinhard [*Anal. Biochem.* 1992, 205: 257-262].

in vitro: The enzyme source is a crude rat kidney mitochondrial preparation which, taken up in the ratio 1:70 (weight/volume) in a potassium phosphate buffer of pH 7.4, containing EGTA, is kept in the frozen state at -80°C until used. The enzyme test for the *in vitro* determination differs from the *ex vivo* determination described hereinafter by the use of the mentioned mitochondrial preparation in place of tissue homogenates as the enzyme source and by a pre-incubation of the enzyme with the substances to be tested at 37°C for 15 min.

ex vivo: The substances to be tested are administered orally to male rats of 100-140 g body weight in a dosage of 30 µmol/kg.

The kidneys and a part of the liver are removed from the animals, which are decapitated after 2 hours, and frozen at -80°C until used. In order to measure the enzyme activity, the organs are homogenized in the ratio 1:10 (weight/volume) in sucrose,
 5 containing TRIS/HCl, pH 7.4 and PMSF.

Measurement of the enzyme activity

Scheme of a typical procedure carried out in an incubation tube of
 10 appropriate size or on a microtitre plate:

- 25 µl of the substance to be tested in a suitable concentration (*in vitro*) or homogenization buffer (*ex vivo*)
- 15 - 25 µl of potassium phosphate buffer 0.2M containing 0.4 units of glucose-6-phosphate dehydrogenase
- 25 µl of the mitochondrial preparation (*in vitro*) or of the kidney or liver homogenate (*ex vivo*)
- 20 - pre-incubation: 15 min at 37°C (only *in vitro*)
- 25 µl of the substrate L-kynurenin containing L-³H-3-kynurenin (0.1 µCi)
- 25 100 µmol, magnesium chloride 4 mmol, NADPH 200 µmol, glucose-6-phosphate 3 mmol (concentration data as final concentrations)
- incubation: 10 min (*in vitro*) or 2 min (*ex vivo*) at 37°C on a
 30 shaking machine
- 150 µl of a 10% suspension of active charcoal (Norit A) in water (to remove unreacted labelled substrate)
- 35 - shaking for about one minute
- centrifugation for 4 min at 4000 revolutions/min

- transfer of 50 μ l of the charcoal-free supernatant into a counting vessel
- addition of 150 μ l of an appropriate scintillator to count
5 the radioactivity of the now-tritiated water, which is a measurement of the enzyme activity which exists.

The IC₅₀ value is a measurement of the strength of the *in vitro* enzyme inhibition which is brought about by the tested
10 substances. It is the concentration of test substance which brings about a 50% inhibition of the enzyme activity.

The ED₅₀ value or, where this is not achieved, the percentage inhibition after administration of a single dosage, is a measure-
15 ment of the strength of the *ex vivo* enzyme inhibition which is brought about by the tested substances. The ED₅₀ value is that dosage of test substance which leads to a 50% enzyme inhibition in the investigated tissue homogenates.

Example No. Compound	% of control at 1 μ M	IC ₅₀ [μ M]	% of control 30 μ M/kg p.o in the liver	ED ₅₀ μ Mol/kg p.o. in the liver
3 A		0.04	43.00	
6 B	4.58	0.065	54.00	
8 C	5.00	0.044	23.00	9.0
D	4.00	0.03	20.00	
21 E	2.00	0.026	10.00	4.7
32 F	2.50	0.043		17.0
41 G	18.00	0.050		17.0
42 H	1.40	0.015		4.6
46 I	4.70	0.022		5.3

A 4-Methyl-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzene-sulphonamide

5 B N-[4-(3,4-Dimethoxy-phenyl)-thiazol-2-yl]-4-methyl-benzenesulphonamide

C 4-Methoxy-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzene-sulphonamide

D Naphthalene-2-sulphonic acid [4-(3-nitro-phenyl)-thiazol-

2-yl)-amide

E 3,4-Dimethoxy-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzenesulphonamide

F N-[4-(2-Fluoro-5-trifluoromethyl-phenyl)-thiazol-2-yl]-4-methyl-benzenesulphonamide

G N-[4-(2-Fluoro-5-trifluoromethyl-phenyl)-thiazol-2-yl]-4-methoxy-benzenesulphonamide

H 4-Amino-N-[4-(2-fluoro-5-trifluoromethyl-phenyl)-thiazol-2-yl]-benzene sulphonamide

I 3,4-Dimethoxy-N-[4-(2-fluoro-5-trifluoromethyl-phenyl)-thiazol-2-yl]-benzenesulphonamide

As mentioned above, some novel compounds also have an antibacterial activity, for example against *Staphylococcus aureus* and *Streptococcus pyogenes*.

From the following Table it will be evident that the antibacterial activity of two chosen compounds is comparable with that of the known antibacterial compound sulfamethoxazole (SMZ). Moreover, comparison was made with trimethoprim (TMP).

Type	Strain	BCB	TMP	SMZ	Example 42	Example 46
<i>Staphylococcus aureus</i>	ATCC 25923	1003/04	0.5	32	16	32
<i>Enterococcus faecalis</i>	ATCC 29212	1003/28	0.125	>256	>256	>256
<i>Streptococcus pneumoniae</i>	ATCC 49619		4	>256	>256	>256
<i>Streptococcus pyogenes</i>	B15	1003/35	2	16	16	64
<i>Listeria monocytogenes</i>	BK23	1003/55	0.25	>256	>256	>256
<i>Escherichia coli</i>	ATCC25922	1001/04	1	128	256	>256
<i>Pseudomonas aeruginosa</i>	BA	1004/01	8	>256	>256	>256

Method for the determination of antibacterial activity

The minimum inhibitory concentration (MIC in $\mu\text{g/ml}$) was determined by the microdilution method in which an Isosensotest bouillon (Oxoid) was used and was complemented with 3% horse blood for *Streptococcus* and *Listeria*. The inoculation amount was approximately 5×10^5 CFU/ml. After incubation at 37°C for 18 h the plates were evaluated at 650 nm. The MIC was determined as

the lowest concentration of active substance which brought about a growth inhibition of $\geq 80\%$ compared to the control.

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

The compounds of formula I and pharmaceutically acceptable salts thereof can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active ingredient no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar, glucose and the like. Adjuvants such as alcohols, polyols, glycerol, vegetable oils and the like can be used for aqueous injection solutions of water-soluble salts of compounds of formula I, but are usually not necessary. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

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

As mentioned earlier, medicaments containing a novel compound of formula I or a pharmaceutically acceptable salt thereof and a therapeutically inert excipient are also an object of the present invention, furthermore also a process for the
5 production of such medicaments which comprises bringing one or more novel compounds of formula I or pharmaceutically acceptable salts thereof and, if desired, one or more other therapeutically valuable substances into a galenical administration form together with one or more therapeutically
10 inert carriers. The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of intravenous administration a daily dosage of about 1 mg to 1000 mg should be appropriate.

15

The object of the invention in its broadest aspect is, as mentioned earlier, the use of compounds of formula I and of pharmaceutically usable salts thereof in the control or prevention of neurodegenerative diseases, neurological disorders resulting
20 from an activation of the immune system or psychiatric illnesses and, respectively, for the production of corresponding medicaments.

The following Examples illustrate the present invention in
25 more detail, but are not intended to limit its scope in any manner.

Example 1

N-[4-(4-Hydroxy-3-methyl-phenyl)-thiazol-2-yl]-4-methyl-
30 benzenesulphonamide

A solution of 26 g of 4-toluenesulphonyl-thiourea in 225 ml of ethanol was treated with 25.9 g of 2-bromo-1-(4-hydroxy-3-methyl-phenyl)-ethanone, left to stand at room
35 temperature for 3 days and then boiled for a brief period. The reaction mixture was evaporated to dryness in a vacuum and subsequently partitioned between water and ethyl acetate. The aqueous phase was extracted once with ethyl acetate, the organic

phases were combined, dried with sodium sulphate and concentrated. The residue was chromatographed on 500 g of Kieselgel 60 with ethyl acetate/hexane (1:1) as the eluent. The product-containing fractions were concentrated and, after
5 recrystallization from 50% ethanol, yielded 10.1 g of N-[4-(4-hydroxy-3-methyl-phenyl)-thiazol-2-yl]-4-methyl-benzene-sulphonamide as colourless crystals.

M.p.: 168-170°C (dec).

10

Example 2

N-[4-(3-cyano-phenyl)-thiazol-2-yl]-4-methyl-benzene-sulphonamide

15

A mixture of 0.5 g of 3-(2-amino-thiazol-4-yl)-benzonitrile with 0.52 g of p-toluenesulphonyl chloride was stirred overnight with 2 ml of pyridine. The resulting, red coloured suspension was poured into 50 ml of 1N hydrochloric acid and the solid
20 which thereby separated was filtered off and dissolved in a mixture of 20 ml of ethanol and 20 ml of 2N sodium hydroxide solution. After the addition of 0.4 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. The product
25 separated upon neutralization with concentrated hydrochloric acid. Recrystallization from 80 ml of 50% ethanol yielded 0.35 g of N-[4-(3-cyano-phenyl)-thiazol-2-yl]-4-methyl-benzenesulphonamide as colourless crystals.

30 M.p.: > 250°C

Example 34-Methyl-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzene-sulphonamide

5

A mixture of 0.5 g of 4-(3-nitro-phenyl)-thiazol-2-ylamine hydrochloride with 0.42 g of p-toluenesulphonyl chloride was stirred overnight with 2 ml of pyridine. The resulting, red coloured suspension was poured into 50 ml of 1N hydrochloric acid and the solid which thereby separated was filtered off and dissolved in a mixture of 10 ml of ethanol and 10 ml of 2N sodium hydroxide solution. After the addition of 0.4 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. The product separated upon neutralization with concentrated hydrochloric acid. Recrystallization from 40 ml of 50% ethanol yielded 0.35 g of 4-methyl-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzenesulphonamide as yellowish crystals.

20 M.p.: 187-189°C

Example 4N-[4-(4-Benzyloxy-3-methoxy-phenyl)-thiazol-2-yl]-benzene-sulphonamide

25

A mixture of 0.5 g of 4-(4-benzyloxy-3-methoxy-phenyl)-thiazol-2-ylamine hydrobromide with 0.27 g of p-toluene-sulphonyl chloride was stirred overnight with 2 ml of pyridine. The resulting, red coloured solution was poured into 50 ml of 1N hydrochloric acid and extracted three times with 50 ml of methylene chloride each time. The organic extracts were combined, dried with magnesium sulphate and concentrated. The residue was chromatographed on 40 g of Kieselgel 60 with diethyl ether/hexane (2:1) as the eluent. Concentration of the product-containing fractions yielded 0.35 g of N-[4-(4-benzyloxy-3-methoxy-phenyl)-thiazol-2-yl]-benzenesulphonamide as colourless crystals.

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M.p.: 152-155°C

Example 5

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N-[4-(3,4-Bis-benzyloxy-phenyl)-thiazol-2-yl]-4-methyl-
benzenesulphonamide

A mixture of 0.5 g of 4-(3,4-bis-benzyloxy-phenyl)-thiazol-
10 2-ylamine hydrobromide with 0.23 g of p-toluenesulphonyl
chloride was stirred overnight with 2 ml of pyridine. The
resulting, red coloured solution was poured into 50 ml of 1N
hydrochloric acid and extracted three times with 50 ml of
methylene chloride each time. The organic extracts were
15 combined, dried with magnesium sulphate and concentrated. The
residue was dissolved in a mixture of 20 ml of ethanol and 15 ml
of 2N sodium hydroxide solution. After the addition of 0.4 g of
active charcoal the mixture was stirred at room temperature for
30 minutes and subsequently the active charcoal was filtered
20 off. The product separated upon neutralization with concentrated
hydrochloric acid. Recrystallization from 50 ml of 60% ethanol
yielded 0.33 g of N-[4-(3,4-bis-benzyloxy-phenyl)-thiazol-2-yl]-
4-methyl-benzenesulphonamide as colourless crystals.

25 M.p.: 158-161°C

Example 6

N-[4-(3,4-Dimethoxy-phenyl)-thiazol-2-yl]-4-methyl-
30 benzenesulphonamide

A mixture of 0.5 g of 4-(3,4-dimethoxy-phenyl)-thiazol-2-
ylamine hydrobromide with 0.33 g of p-toluenesulphonyl chloride
was stirred overnight with 2 ml of pyridine. The resulting, red
35 coloured solution was poured into 50 ml of 1N hydrochloric acid
and extracted three times with 50 ml of methylene chloride each
time. The organic extracts were combined, dried with magnesium
sulphate and concentrated. The residue was chromatographed on

35 g of Kieselgel 60 with diethyl ether as the eluent. The product-containing fractions were concentrated, dissolved in 40 ml of 50% ethanol by the addition of a small amount of 2N sodium hydroxide solution and precipitated with 2N hydrochloric acid at pH 6. 0.4 g of N-[4-(3,4-dimethoxy-phenyl)-thiazol-2-yl]-4-methyl-benzenesulphonamide was obtained as colourless crystals.

M.p.: 85-87°C (dec.)

Example 7

N-[4-(4-Methoxy-3-methyl-phenyl)-thiazol-2-yl]-4-methyl-benzenesulphonamide

A mixture of 0.5 g of 4-(4-methoxy-3-methyl-phenyl)-thiazol-2-ylamine hydrobromide with 0.5 g of p-toluenesulphonyl chloride was stirred overnight with 2 ml of pyridine. The resulting, red coloured solution was poured into 50 ml of 1N hydrochloric acid and the solid which thereby separated was filtered off and dissolved in a hot mixture of 20 ml of ethanol and 50 ml of water. 0.06 g of N-[4-(4-methoxy-3-methyl-phenyl)-thiazol-2-yl]-4-methyl-benzenesulphonamide separated as beige crystals upon cooling.

M.p.: 94-96°C

Example 8

4-Methoxy-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzenesulphonamide

A mixture of 0.5 g of 4-(3-nitro-phenyl)-thiazol-2-ylamine hydrochloride with 0.44 g of 4-methoxybenzenesulphonyl chloride was stirred overnight with 2 ml of pyridine. The resulting, red coloured suspension was poured into 50 ml of 1N hydrochloric acid and the solid which thereby separated was filtered off and dissolved in a mixture of 40 ml of ethanol and 20 ml of 2N

sodium hydroxide solution. After the addition of 0.5 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. The product separated upon neutralization with concentrated
5 hydrochloric acid. Recrystallization from 40 ml of 50% ethanol yielded 0.31 g of 4-methoxy-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzenesulphonamide as yellowish crystals.

M.p.: 157-159°C

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Example 9

4-Chloro-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzene-sulphonamide

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A mixture of 0.5 g of 4-(3-nitro-phenyl)-thiazol-2-ylamine hydrochloride with 0.45 g of 4-chlorobenzenesulphonyl chloride was stirred overnight with 2 ml of pyridine. The resulting, red coloured suspension was poured into 50 ml of 1N hydrochloric
20 acid and the solid which thereby separated was filtered off and dissolved in a mixture of 40 ml of ethanol and 20 ml of 2N sodium hydroxide solution. After the addition of 0.5 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered
25 off. The product separated upon neutralization with concentrated hydrochloric acid. Recrystallization from 40 ml of 50% ethanol yielded 0.43 g of 4-chloro-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzenesulphonamide as colourless crystals.

30 M.p.: 195-197°C

Example 10

3,4-Dichloro-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzene-sulphonamide

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A mixture of 0.5 g of 4-(3-nitro-phenyl)-thiazol-2-ylamine hydrochloride with 0.52 g of 3,4-dichlorobenzenesulphonyl

chloride was stirred overnight with 2 ml of pyridine. The resulting, red coloured suspension was poured into 25 ml of 1N hydrochloric acid and the solid which thereby separated was filtered off and dissolved in a mixture of 30 ml of ethanol and 20 ml of 2N sodium hydroxide solution. After the addition of 0.5 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. The product separated upon neutralization with concentrated hydrochloric acid. Recrystallization from 80 ml of 50% ethanol yielded 0.39 g of 3,4-dichloro-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzenesulphonamide as yellowish crystals.

M.p.: 189-191°C

Example 11

Benzo[1,3]dioxol-5-sulphonic acid [4-(3-nitro-phenyl)-thiazol-2-yl]-amide

A mixture of 0.5 g 4-(3-nitro-phenyl)-thiazol-2-ylamine hydrochloride with 0.52 g of benzo[1,3]dioxol-5-sulphonyl chloride was stirred overnight with 2 ml of pyridine. The resulting, red coloured suspension was poured into 25 ml of 1N hydrochloric acid and the solid which thereby separated was filtered off and dissolved in a mixture of 30 ml of ethanol and 20 ml of 2N sodium hydroxide solution. After the addition of 0.5 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. The product separated upon neutralization with concentrated hydrochloric acid. Recrystallization from 100 ml of 60% ethanol yielded 0.30 g of benzo[1,3]dioxol-5-sulphonic acid [4-(3-nitro-phenyl)-thiazol-2-yl]-amide as yellowish crystals.

M.p.: 221-224°C

Example 125-Isopropyl-pyridine-2-sulphonic acid [4-(3-nitro-phenyl)-thiazol-2-yl]-amide

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A mixture of 0.5 g of 4-(3-nitro-phenyl)-thiazol-2-ylamine hydrochloride with 0.46 g of 5-isopropyl-pyridine-2-sulphonyl chloride was stirred overnight with 2 ml of pyridine. The resulting, red coloured suspension was poured into 25 ml of 1N hydrochloric acid and the solid which thereby separated was filtered off and dissolved in a mixture of 30 ml of ethanol and 20 ml of 2N sodium hydroxide solution. After the addition of 0.5 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. The product separated upon neutralization with concentrated hydrochloric acid. Recrystallization from 40 ml of ethanol and 20 ml of ethyl acetate yielded 0.31 g of 5-isopropyl-pyridine-2-sulphonic acid [4-(3-nitro-phenyl)-thiazol-2-yl]-amide as yellowish crystals.

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M.p.: 208-210°C

Example 133,5-Dichloro-4-(4-nitro-phenoxy)-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzenesulphonamide

A mixture of 0.26 g of 4-(3-nitro-phenyl)-thiazol-2-ylamine hydrochloride with 0.42 g of 3,5-dichloro-4-nitro-phenoxybenzenesulphonyl chloride was stirred overnight with 2 ml of pyridine. The resulting, red coloured suspension was poured into 50 ml of 1N hydrochloric acid and the solid which thereby separated was filtered off and dissolved in a mixture of 50 ml of ethanol and 20 ml of 2N sodium hydroxide solution. After the addition of 0.5 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. The product separated upon neutralization with concentrated hydrochloric acid. Recrystal-

lization from 50 ml of ethanol and 20 ml of ethyl acetate yielded 0.11 g of 3,5-dichloro-4-(4-nitro-phenoxy)-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzenesulphonamide as yellowish crystals.

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M.p.: >250°C

Example 14

10 N-[4-(4-Chloro-phenyl)-thiazol-2-yl]-4-methyl-benzene-sulphonamide

A mixture of 0.3 g of 4-(4-chlorophenyl)-thiazol-2-ylamine hydrobromide with 0.22 g of p-toluenesulphonyl chloride was
15 stirred overnight with 2 ml of pyridine. The resulting, red coloured suspension was poured into 30 ml of 1N hydrochloric acid and the solid which thereby separated was filtered off and dissolved in a hot mixture of 20 ml of ethanol and 30 ml of water. 0.05 g of N-[4-(4-chlorophenyl)-thiazol-2-yl]-4-methyl-
20 benzenesulphonamide separated as colourless crystals upon cooling.

M.p.: 237-239°C

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Example 15

N-[4-(4-Bromo-phenyl)-thiazol-2-yl]-4-methyl-benzene-sulphonamide

A mixture of 4.0 g of 4-(4-bromophenyl)-thiazol-2-ylamine hydrobromide with 2.5 g of p-toluenesulphonyl chloride was stirred overnight with 15 ml of pyridine. The resulting, red coloured suspension was poured into 180 ml of 1N hydrochloric acid and the solid which thereby separated was filtered off and
35 chromatographed on 100 g of Kieselgel 60 with diethyl ether/hexane/methylene chloride (1:1:1) as the eluent. The product-containing fractions were concentrated and the residue was recrystallized twice from 60% ethanol. 0.8 g of N-[4-(4-bromo-

phenyl)-thiazol-2-yl]-4-methyl-benzenesulphonamide separated as colourless crystals upon cooling.

M.p.: 227-230°C

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Example 16

N-[4-(3-Nitro-phenyl)-thiazol-2-yl]-benzenesulphonamide

10 A mixture of 0.5 g of 4-(3-nitro-phenyl)-thiazol-2-ylamine hydrobromide with 0.21 g of benzenesulphonyl chloride was stirred overnight with 2 ml of pyridine. The resulting, red coloured suspension was poured into 25 ml of 1N hydrochloric acid and the solid which thereby separated was filtered off and
15 dissolved in a mixture of 20 ml of ethanol and 20 ml of 2N sodium hydroxide solution. After the addition of 0.5 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. The product separated as an oil upon neutralization and was
20 thereupon again treated with active charcoal. The product separated upon renewed neutralization with concentrated hydrochloric acid. Recrystallization from 10 ml of 50% ethanol yielded 0.06 g of N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzene-sulphonamide as yellowish crystals.

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M.p.: 141-142°C

Example 17

4-Cyclohexyl-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzene-sulphonamide

A mixture of 0.5 g of 4-(3-nitro-phenyl)-thiazol-2-ylamine hydrobromide with 0.46 g of 4-cyclohexyl-benzenesulphonyl
35 chloride was stirred overnight with 2 ml of pyridine. The resulting, red coloured suspension was poured into 25 ml of 1N hydrochloric acid and the organic phase was separated and dissolved in a mixture of 20 ml of ethanol and 20 ml of 2N

sodium hydroxide solution. After the addition of 0.5 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. The product separated as an oil upon neutralization.

- 5 Thereupon, 20 ml of ethanol were added, the mixture was boiled and insoluble material was filtered off. Crystals separated upon cooling and, after recrystallization from 40 ml of 50% ethanol, yielded 0.15 g of 4-cyclohexyl-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzenesulphonamide as beige crystals.

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M.p.: 180-182°C

Example 18

15 4-Isopropyl-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzene-sulphonamide

- A mixture of 0.5 g of 4-(3-nitro-phenyl)-thiazol-2-ylamine hydrobromide with 0.36 g of 4-isopropylbenzenesulphonyl
20 chloride was stirred overnight with 2 ml of pyridine. The resulting, red coloured suspension was poured into 25 ml of 1N hydrochloric acid and the organic phase was separated and dissolved in a mixture of 20 ml of ethanol and 20 ml of 2N sodium hydroxide solution. After the addition of 0.5 g of active
25 charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. The product separated as an oil upon neutralization. Thereupon, the mixture was boiled with 0.5 g of active charcoal and the active charcoal and insoluble constituents were filtered
30 off. Crystals separated upon cooling and, after recrystallization from 40 ml of 50% ethanol, yielded 0.17 g of 4-isopropyl-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzenesulphonamide as colourless crystals.

35 M.p.: 144-145°C

Example 194-Methyl-N-[4-(4-nitro-phenyl)-thiazol-2-yl]-benzene-sulphonamide

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A mixture of 0.5 g of 4-(4-nitro-phenyl)-thiazol-2-ylamine hydrobromide with 0.35 g of p-toluenesulphonyl chloride was stirred overnight with 2 ml of pyridine. The resulting, red coloured suspension was poured into 30 ml of 1N hydrochloric acid and the mixture was extracted three times with 100 ml of ethyl acetate each time. The organic phases were combined, dried with magnesium sulphate and the solvent was removed on a rotary evaporator. The residue was chromatographed on 60 g of Kieselgel 60 with diethyl ether/ethyl acetate (1:1) as the eluent. The product-containing fractions were concentrated and the residue was digested with a mixture of 20 ml of ethanol and 20 ml of 2N sodium hydroxide solution. The product separated upon neutralization of the filtrate with concentrated hydrochloric acid. Recrystallization from 50 ml of 60% ethanol yielded 0.10 g of 4-methyl-N-[4-(4-nitro-phenyl)-thiazol-2-yl]-benzene-sulphonamide as yellowish crystals.

M.p.: >250°C

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Example 20N-[4-[4-(3-Nitro-phenyl)-thiazol-2-ylsulphamoyl]-phenyl]-acetamide

30

A mixture of 0.5 g of 4-(3-nitro-phenyl)-thiazol-2-ylamine hydrobromide with 0.43 g of 4-acetamino-benzenesulphonyl chloride was stirred overnight with 2 ml of pyridine. The resulting, red coloured suspension was poured into 30 ml of 1N hydrochloric acid and the solid which thereby separated was filtered off and dissolved in a mixture of 20 ml of ethanol and 20 ml of 2N sodium hydroxide solution. After the addition of 0.5 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal

was filtered off. 0.60 g of N-{4-[4-(3-nitro-phenyl)-thiazol-2-ylsulphamoyl]-phenyl}-acetamide separated as yellowish crystals upon neutralization with concentrated hydrochloric acid.

5 M.p.: >250°C

Example 21

3,4-Dimethoxy-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzenesulphonamide

A mixture of 0.5 g of 4-(3-nitro-phenyl)-thiazol-2-ylamine hydrobromide with 0.43 g of 3,4-dimethoxy-benzenesulphonyl chloride was stirred overnight with 2 ml of pyridine. The resulting, red coloured suspension was poured into 30 ml of 1N hydrochloric acid and the organic phase was separated and dissolved in a mixture of 20 ml of ethanol and 20 ml of 2N sodium hydroxide solution. After the addition of 0.5 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. The product separated as an oil upon neutralization and was thereupon treated once more with active charcoal. The product separated upon renewed neutralization with concentrated hydrochloric acid. Recrystallization from 25 ml of 60% ethanol yielded 0.12 g of 3,4-dimethoxy-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzenesulphonamide as colourless crystals.

M.p.: 185°C

Example 22

5-tert-Butyl-thiophene-2-sulphonic acid [4-(3-nitro-phenyl)-thiazol-2-yl]-amide

A mixture of 0.5 g of 4-(3-nitro-phenyl)-thiazol-2-ylamine hydrobromide with 0.43 g of 5-tert-butyl-thiophene-2-sulphonyl chloride was stirred overnight with 2 ml of pyridine. The resulting, red coloured suspension was poured into 30 ml of 1N

hydrochloric acid and the mixture was extracted three times with 30 ml of ethyl acetate each time. The organic phases were combined, dried with magnesium sulphate and the solvent was removed on a rotary evaporator. The residue was chromatographed on 50 g of Kieselgel 60 with ethyl acetate/hexane (1:2) as the eluent. The product-containing fractions were concentrated and the residue was dissolved in a mixture of 20 ml of ethanol and 20 ml of 2N sodium hydroxide solution. After the addition of 0.4 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. 0.20 g of 5-tert-butyl-thiophene-2-sulphonic acid [4-(3-nitro-phenyl)-thiazol-2-yl]-amide separated as yellowish crystals after neutralization with concentrated hydrochloric acid and repeated boiling.

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M.p.: 176-178°C

Example 23

20 N-[4-(4-Methoxy-phenyl)-thiazol-2-yl]-4-methyl-benzene-sulphonamide

A mixture of 0.5 g of 4-(4-methoxy-phenyl)-thiazol-2-ylamine hydrobromide with 0.37 g of p-toluenesulphonyl chloride was stirred overnight with 2 ml of pyridine. The resulting, red coloured suspension was poured into 30 ml of 1N hydrochloric acid and the mixture was extracted twice with 40 ml of ethyl acetate each time. The organic phases were combined, dried with magnesium sulphate and the solvent was removed on a rotary evaporator. The residue was dissolved in a mixture of 20 ml of ethanol and 20 ml of 2N sodium hydroxide solution. After the addition of 0.4 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. The product separated upon neutralization with concentrated hydrochloric acid. Recrystallization from 30 ml of 50% ethanol yielded 0.24 g of N-[4-(4-methoxy-phenyl)-thiazol-2-yl]-4-methyl-benzenesulphonamide as beige crystals.

M.p.: 85-88°C (dec.)

Example 24

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4-Methyl-N-[4-(3-trifluoromethyl-phenyl)-thiazol-2-yl]-benzenesulphonamide

A mixture of 0.5 g of 4-(3-trifluoromethyl-phenyl)-thiazol-
10 2-ylamine hydrobromide with 0.42 g of p-toluenesulphonyl
chloride was stirred overnight with 2 ml of pyridine. The
resulting, red coloured suspension was poured into 30 ml of 1N
hydrochloric acid and the mixture was extracted twice with
40 ml of ethyl acetate each time. The organic phases were
15 combined, dried with magnesium sulphate and the solvent was
removed on a rotary evaporator. The residue was dissolved in a
mixture of 20 ml of ethanol and 20 ml of 2N sodium hydroxide
solution. After the addition of 0.4 g of active charcoal the
mixture was stirred at room temperature for 30 minutes and
20 subsequently the active charcoal was filtered off. 0.23 g of 4-
methyl-N-[4-(3-trifluoromethyl-phenyl)-thiazol-2-yl]-benzene-
sulphonamide separated as colourless crystals upon neutral-
ization with concentrated hydrochloric acid.

25 M.p.: 157-159°C

Example 25

4-Methyl-N-[4-(4-methyl-phenyl)-thiazol-2-yl]-benzene- 30 sulphonamide

A mixture of 0.5 g 4-(4-methyl-phenyl)-thiazol-2-ylamine
hydrobromide with 0.39 g of p-toluenesulphonyl chloride was
stirred overnight with 2 ml of pyridine. The resulting, red
35 coloured suspension was poured into 30 ml of 1N hydrochloric
acid and the mixture was extracted twice with 50 ml of ethyl
acetate each time. The organic phases were combined, dried with
magnesium sulphate and the solvent was removed on a rotary

evaporator. The residue was dissolved in a mixture of 20 ml of ethanol and 20 ml of 2N sodium hydroxide solution. After the addition of 0.4 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. 0.46 g of 4-methyl-N-[4-(4-methyl-phenyl)-thiazol-2-yl]-benzenesulphonamide was obtained as colourless crystals upon neutralization with concentrated hydrochloric acid.

10 M.p.: 186-189°C

Example 26

15 4-Methyl-N-[4-(2-nitro-phenyl)-thiazol-2-yl]-benzene-sulphonamide

A mixture of 0.5 g of 4-(2-nitro-phenyl)-thiazol-2-ylamine hydrobromide with 0.47 g of p-toluenesulphonyl chloride was stirred overnight with 2 ml of pyridine. The resulting, red coloured suspension was poured into 30 ml of 1N hydrochloric acid and extracted twice with 40 ml of ethyl acetate each time. The organic extracts were combined, dried with magnesium sulphate and concentrated. The residue was dissolved in a mixture of 30 ml of ethanol and 20 ml of 2N sodium hydroxide solution. After the addition of 0.4 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. After neutralization with concentrated hydrochloric acid and boiling there separated, upon cooling, 0.58 g of 4-methyl-N-[4-(2-nitro-phenyl)-thiazol-2-yl]-benzenesulphonamide as yellow crystals.

M.p.: 172-174°C

Example 274-Methyl-N-(4-naphthalen-1-yl-thiazol-2-yl)-benzene-sulphonamide

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A mixture of 0.5 g of 4-(1-naphthyl)-thiazol-2-ylamine hydrobromide with 0.34 g of p-toluenesulphonyl chloride was stirred overnight with 2 ml of pyridine. The resulting, red coloured suspension was poured into 30 ml of 1N hydrochloric acid and extracted twice with 40 ml of ethyl acetate each time. The organic extracts were combined, dried with magnesium sulphate and concentrated. The residue was dissolved in a mixture of 20 ml of ethanol and 20 ml of 2N sodium hydroxide solution. After the addition of 0.4 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. The product separated upon neutralization with concentrated hydrochloric acid. Recrystallization from 60 ml of 50% ethanol yielded 0.46 g of 4-methyl-N-(4-naphthalen-1-yl-thiazol-2-yl)-benzene-sulphonamide as colourless crystals.

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M.p.: 196-197°C

Example 28

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N-[4-(3,4-Dichloro-phenyl)-thiazol-2-yl]-4-methyl-benzene-sulphonamide

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A mixture of 0.5 g of 4-(3,4-dichloro-phenyl)-thiazol-2-ylamine hydrobromide with 0.50 g of p-toluenesulphonyl chloride was stirred overnight with 2 ml of pyridine. The resulting, red coloured suspension was poured into 30 ml of 1N hydrochloric acid and the solid which thereby separated was filtered off and dissolved in a mixture of 20 ml of ethanol and 20 ml of 2N sodium hydroxide solution. After the addition of 0.4 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. 0.33 g of N-[4-(3,4-dichloro-phenyl)-thiazol-2-yl]-4-

methyl-benzenesulphonamide was obtained as colourless crystals upon neutralization with concentrated hydrochloric acid.

M.p.: 205-206°C

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Example 29

N-[4-(2,4-Dichloro-phenyl)-thiazol-2-yl]-4-methyl-benzene-sulphonamide

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A mixture of 0.5 g of 4-(2,4-dichloro-phenyl)-thiazol-2-ylamine hydrobromide with 0.32 g of p-toluenesulphonyl chloride was stirred overnight with 2 ml of pyridine. The resulting, red coloured suspension was poured into 30 ml of 1N hydrochloric acid and extracted three times with 40 ml of ethyl acetate each time. The organic extracts were combined, dried with magnesium sulphate and concentrated. The residue was dissolved in a mixture of 20 ml of ethanol and 20 ml of 2N sodium hydroxide solution. After the addition of 0.4 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. 0.50 g of N-[4-(2,4-dichloro-phenyl)-thiazol-2-yl]-4-methyl-benzenesulphonamide separated as colourless crystals upon neutralization with concentrated hydrochloric acid.

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M.p.: 218-219°C

Example 30

N-[4-(3-Bromo-phenyl)-thiazol-2-yl]-4-methyl-benzene-sulphonamide

A mixture of 0.5 g of 4-(3-bromo-phenyl)-thiazol-2-ylamine hydrobromide with 0.31 g of p-toluenesulphonyl chloride was stirred overnight with 2 ml of pyridine. The resulting, red coloured suspension was poured into 30 ml of 1N hydrochloric acid and the solid which thereby separated was filtered off and dissolved in a mixture of 20 ml of ethanol and 20 ml of 2N

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sodium hydroxide solution. After the addition of 0.4 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. 0.40 g of N-[4-(3-bromo-phenyl)-thiazol-2-yl]-4-methyl-benzenesulphonamide separated as colourless crystals upon neutralization with concentrated hydrochloric acid.

M.p.: 199-200°C

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Example 31

4-Amino-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzenesulphonamide

0.47 g of N-{4-[4-(3-nitro-phenyl)-thiazol-2-yl-sulphamoyl]-phenyl}-acetamide was suspended in 10 ml of 6N hydrochloric acid and heated to boiling overnight. The cooled mixture was treated with 35 ml of 2N sodium hydroxide solution. After the addition of 0.4 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. The product separated upon neutralization with concentrated hydrochloric acid. Recrystallization from 50 ml of 40% ethanol yielded 0.16 g of 4-amino-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzenesulphonamide as yellowish crystals.

M.p.: 191-193°C

Example 32

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N-[4-(2-Fluoro-5-trifluoromethyl-phenyl)-thiazol-2-yl]-4-methyl-benzenesulphonamide

A mixture of 0.5 g of 4-(2-fluoro-5-trifluoromethyl-phenyl)-thiazol-2-ylamine hydrobromide with 0.30 g of p-toluenesulphonyl chloride was stirred for 3 hours with 2 ml of pyridine. The resulting, red coloured suspension was poured into 30 ml of 1N hydrochloric acid and the mixture was extracted

with ethyl acetate. The organic phase was dried with magnesium sulphate and concentrated. The residue was dissolved in a mixture of 20 ml of ethanol and 20 ml of 2N sodium hydroxide solution. After the addition of 0.3 g of active charcoal the
5 mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. 0.36 g of N-[4-(2-fluoro-5-trifluoromethyl-phenyl)-thiazol-2-yl]-4-methyl-benzenesulphonamide separated as colourless crystals upon neutralization with concentrated hydrochloric acid.

10 M.p.: 136-140°C

Example 33

15 4-Benzyloxy-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzene-sulphonamide

A mixture of 0.5 g of 4-(3-nitro-phenyl)-thiazol-2-ylamine hydrobromide with 0.51 g of 4-phenylmethoxy-benzenesulphonyl
20 chloride was stirred overnight with 2 ml of pyridine. The resulting, red coloured suspension was poured into 30 ml of 1N hydrochloric acid. The mixture was extracted three times with ethyl acetate. The organic phases were combined, dried with magnesium sulphate and freed from solvent. The residue was
25 boiled with 30 ml of ethyl acetate, insoluble constituents were filtered off and the solution was treated at boiling with 20 ml of hexane. 0.5 g of 4-benzyloxy-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzenesulphonamide separated as beige crystals upon cooling.

30 M.p.: 214-216°C

Example 34N-[4-(3-Nitro-phenyl)-thiazol-2-yl]-C-phenyl-methane-sulphonamide

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A mixture of 0.5 g of 4-(3-nitro-phenyl)-thiazol-2-ylamine hydrobromide with 0.35 g of phenylmethanesulphonyl chloride was stirred overnight with 2 ml of pyridine. The resulting, red coloured suspension was poured into 30 ml of 1N hydrochloric acid and the solid which thereby separated was filtered off and dissolved in a mixture of 25 ml of ethanol and 20 ml of 2N sodium hydroxide solution. After the addition of 0.4 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. After neutralization with concentrated hydrochloric acid the mixture was concentrated and the aqueous residue was extracted twice with ethyl acetate. The organic phases were combined, dried with magnesium sulphate and freed from solvent. The residue was chromatographed on 30 g of Kieselgel 60 with ethyl acetate/hexane (1:2) as the eluent. The product-containing fractions were concentrated. Recrystallization of the residue from 5 ml of ethyl acetate yielded 60 mg of N-[4-(3-nitro-phenyl)-thiazol-2-yl]-C-phenyl-methanesulphonamide as colourless crystals.

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M.p.: 219-221°C

Example 35N-[4-(4-Cyclohexyl-phenyl)-thiazol-2-yl]-4-methyl-benzene-sulphonamide

A mixture of 0.5 g of 4-(4-cyclohexyl-phenyl)-thiazol-2-ylamine hydrobromide with 0.31 g of p-toluenesulphonyl chloride was stirred for 3 hours with 2 ml of pyridine. The resulting, red coloured suspension was poured into 30 ml of 1N hydrochloric acid and the mixture was extracted with ethyl acetate. The organic phase was dried with magnesium sulphate and

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concentrated. The residue was dissolved in a mixture of 20 ml of ethanol and 20 ml of 2N sodium hydroxide solution. After the addition of 0.5 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. The product separated in amorphous form upon neutralization with concentrated hydrochloric acid. After chromatography on 70 g of Kieselgel 60 with ethyl acetate/hexane (1:2) the product-containing fractions were concentrated. Recrystallization from 50% ethanol yielded 0.22 g of N-[4-(4-cyclohexyl-phenyl)-thiazol-2-yl]-4-methyl-benzenesulphonamide as colourless crystals.

M.p.: 197-199°C

15

Example 36

N-[4-(3-Fluoro-5-trifluoromethyl-phenyl)-thiazol-2-yl]-4-methyl-benzenesulphonamide

A mixture of 0.5 g of 4-(3-fluoro-5-trifluoromethyl-phenyl)-thiazol-2-ylamine hydrobromide with 0.34 g of p-toluenesulphonyl chloride was stirred overnight with 2 ml of pyridine. The resulting, red coloured suspension was poured into 30 ml of 1N hydrochloric acid and the mixture was extracted with ethyl acetate. The organic phase was dried with magnesium sulphate and concentrated. The residue was dissolved in a mixture of 20 ml of ethanol and 20 ml of 2N sodium hydroxide solution. After the addition of 0.4 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. 0.38 g of N-[4-(3-fluoro-5-trifluoromethyl-phenyl)-thiazol-2-yl]-4-methyl-benzenesulphonamide separated as colourless crystals upon neutralization with concentrated hydrochloric acid.

M.p.: 165-167°C

Example 37N-[4-(2-Benzyloxy-phenyl)-thiazol-2-yl]-4-methyl-benzene-sulphonamide

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A mixture of 0.5 g of 4-(2-benzyloxy-phenyl)-thiazol-2-ylamine hydrobromide with 0.29 g of p-toluenesulphonyl chloride was stirred for 2 h with 2 ml of pyridine. The resulting, red coloured suspension was poured into 30 ml of 1N hydrochloric acid and the mixture was extracted with ethyl acetate. The organic phase was dried with magnesium sulphate and concentrated. The residue was dissolved in a mixture of 20 ml of ethanol and 20 ml of 2N sodium hydroxide solution. After the addition of 0.4 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. After neutralization with concentrated hydrochloric acid the mixture was concentrated and the aqueous residue was extracted twice with ethyl acetate. The organic phases were combined, dried with magnesium sulphate and freed from solvent. The residue was chromatographed on 60 g of Kieselgel 60 with ethyl acetate/hexane (1:2) as the eluent. The product-containing fractions were concentrated and yielded 0.28 g of N-[4-(2-benzyloxy-phenyl)-thiazol-2-yl]-4-methyl-benzenesulphonamide as a colourless, amorphous solid.

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NMR (CDCl₃) ppm: 10.5 (bs, 1H), 7.83 (d, 2H), 7.48 ("d", 1H), 7.34 (m, 6H) 7.25 (d, 2H), 7.03 ("t", 2H), 6.59 (s, 1H), 5.26 (s, 2H), 2.40 (s, 3H).

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Example 38N-[4-(3-Benzyloxy-phenyl)-thiazol-2-yl]-4-methyl-benzene-sulphonamide

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A mixture of 3.0 g of 4-(3-benzyloxy-phenyl)-thiazol-2-ylamine hydrobromide with 1.8 g of p-toluenesulphonyl chloride was stirred for 2 h with 12 ml of pyridine. The resulting, red coloured suspension was poured into 100 ml of 2N hydrochloric

acid and the mixture was extracted with ethyl acetate. The organic phase was dried with magnesium sulphate and concentrated. The residue was dissolved in a mixture of 120 ml of ethanol and 120 ml of 2N sodium hydroxide solution. After the
5 addition of 2.4 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. After neutralization with concentrated hydrochloric acid the mixture was concentrated and the aqueous residue was extracted twice with ethyl acetate. The organic
10 phases were combined, dried with magnesium sulphate and freed from solvent. The residue was chromatographed on 300 g of Kieselgel 60 with ethyl acetate/hexane (1:2) as the eluent. The product-containing fractions were concentrated and yielded 2.2 g of N-[4-(3-benzyloxy-phenyl)-thiazol-2-yl]-4-methyl-benzene-
15 sulphonamide as a colourless, amorphous solid.

NMR (CDCl₃) ppm: 9.6 (bs, 1H), 7.85 (d, 2H), 7.36 (m, 6H) 7.24 (d, 2H), 7.01 (m, 3H), 6.50 (s, 1H), 5.08 (s, 2H), 2.39 (s, 3H).

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Example 39

N-[4-(3-Amino-phenyl)-thiazol-2-yl]-4-methyl-benzene-sulphonamide

25 A solution of 1.5 g of 4-methyl-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzenesulphonamide in 150 ml of methanol and 70 ml of ethyl acetate was hydrogenated at room temperature after the addition of 0.15 g of palladium on active charcoal (10%). The catalyst was filtered off and the filtrate was
30 concentrated. Crystallization from ethyl acetate/hexane (1:1) yielded 1.1 g of N-[4-(3-amino-phenyl)-thiazol-2-yl]-4-methyl-benzenesulphonamide as a colourless solid.

M.p.: 180-182°C

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Example 40N-(4-Biphenyl-3-yl-thiazol-2-yl)-4-methyl-benzene-sulphonamide

5

A solution of 0.29 g of N-(4-biphenyl-3-yl-thiazol-2-yl)-N-methoxymethyl-4-methyl-benzenesulphonamide in 6 ml of tetrahydrofuran was stirred at room temperature for 6 hours after the addition of 1.5 ml of 6N hydrochloric acid. The reaction mixture
10 was added to 40 ml of water and extracted with ethyl acetate. The organic phases were combined, dried with magnesium sulphate and concentrated. Recrystallization from 10 ml of 50% ethanol yielded 120 mg of N-(4-biphenyl-3-yl-thiazol-2-yl)-4-methyl-benzenesulphonamide as colourless crystals.

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M.p.: 153-155°C

Example 41

20 N-[4-(2-Fluoro-5-trifluoromethyl-phenyl)-thiazol-2-yl]4-methoxy-benzenesulphonamide

A mixture of 0.5 g of 4-(2-fluoro-5-trifluoromethyl-phenyl)-thiazol-2-ylamine hydrobromide with 0.33 g of
25 4-methoxy-benzenesulphonyl chloride was stirred overnight with 2 ml of pyridine. The resulting, red coloured suspension was poured into 30 ml of 1N hydrochloric acid and the mixture was extracted with ethyl acetate. The organic phase was dried with magnesium sulphate and concentrated. The residue was dissolved
30 in a mixture of 30 ml of ethanol and 20 ml of 2N sodium hydroxide solution. After the addition of 0.5 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. The product separated upon neutralization with concentrated hydrochloric
35 acid. Recrystallization from 30 ml of 50% ethanol yielded 0.26 g of N-[4-(2-fluoro-5-trifluoromethyl-phenyl)-thiazol-2-yl]-4-methoxy-benzenesulphonamide as colourless crystals.

M.p.: 112°C dec.

Example 42

5 4-Amino-N-[4-(2-fluoro-5-trifluoromethyl-phenyl)-thiazol-2-yl]benzenesulphonamide

A mixture of 0.5 g of 4-(2-fluoro-5-trifluoromethyl-phenyl)-thiazol-2-ylamine hydrobromide with 0.38 g of
10 4-acetaminobenzenesulphonyl chloride was stirred for 2 hours with 2 ml of pyridine. The resulting, red coloured suspension was poured into 30 ml of 1N hydrochloric acid and stirred at room temperature for 30 minutes. The separated solid was dissolved in a mixture of 20 ml of ethanol and 20 ml of 2N
15 sodium hydroxide solution. After the addition of 0.5 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. The 4-acetamino-N-[4-(2-fluoro-5-trifluoromethyl-phenyl)-thiazol-2-yl]-benzenesulphonamide, which separated upon
20 neutralization with concentrated hydrochloric acid, was suspended in 9 ml of 6N hydrochloric acid and boiled for 36 hours. The mixture was cooled, treated with 30 ml of ethanol and neutralized with 2N sodium hydroxide solution. Recrystallization of the product, which thereby separated, from 20 ml of
25 50% ethanol yielded 0.21 g of 4-amino-N-[4-(2-fluoro-5-trifluoromethyl-phenyl)-thiazol-2-yl]benzenesulphonamide as colourless crystals.

M.p.: 150-152°C

30

Example 43

N-[4-(4-Benzoyloxy-phenyl)-thiazol-2-yl]4-methyl-benzene-sulphonamide

35

A mixture of 0.5 g of 4-(4-benzyloxy-phenyl)-thiazol-2-ylamine hydrobromide with 0.29 g of p-toluenesulphonyl chloride was stirred for 4 h with 2 ml of pyridine. The resulting, red

coloured suspension was poured into 30 ml of 1N hydrochloric acid and the mixture was extracted with methylene chloride. The organic phase was dried with magnesium sulphate and concentrated. The residue was dissolved in a mixture of 20 ml of ethanol and 20 ml of 2N sodium hydroxide solution. After the addition of 0.7 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. After neutralization with concentrated hydrochloric acid the mixture was concentrated and the residue was chromatographed on 100 g of Kieselgel 60 with diethyl ether as the eluent. The product-containing fractions were concentrated and, after recrystallization from ethyl acetate, yielded 0.22 g of N-[4-(4-benzyloxy-phenyl)-thiazol-2-yl]-4-methyl-benzenesulphonamide as colourless crystals.

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M.p.: 166-167°C.

Example 44

20 4-Methoxy-N-(4-naphthalen-2-yl-thiazol-2-yl)-benzenesulphonamide

A mixture of 0.5 g of 4-(2-naphthyl)-thiazol-2-ylamine hydrobromide with 0.34 g of 4-methoxy-benzenesulphonyl chloride was stirred for 3 hours with 2 ml of pyridine. The resulting, red coloured suspension was poured into 30 ml of 1N hydrochloric acid and extracted with ethyl acetate. The organic phases were combined, dried with magnesium sulphate and freed from solvent. The residue was dissolved in a mixture of 25 ml of ethanol and 20 ml of 2N sodium hydroxide solution. After the addition of 0.5 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. The product separated upon neutralization with concentrated hydrochloric acid. Recrystallization from 10 ml of ethyl acetate and 15 ml of n-hexane yielded 0.19 g of 4-methoxy-N-(4-naphthalen-2-yl-thiazol-2-yl)-benzenesulphonamide as colourless crystals.

M.p.: 163-165°C

Example 45

5 N-[4-(3,4-Dihydroxy-5-nitro-phenyl)-thiazol-2-yl]-4-methyl-
benzenesulphonamide

A mixture of 0.24 g of N-(aminothioxomethyl)-4-methyl-
benzenesulphonamide and 0.2 g of 2-bromo-1-(3,4-dihydroxy-5-
10 nitrophenyl)ethanone was dissolved in 5 ml of ethanol and boiled
under reflux for 1 h. 0.26 g of N-[4-(3,4-dihydroxy-5-nitro-
phenyl)-thiazol-2-yl]-4-methyl-benzenesulphonamide separated
as red crystals upon cooling.

15 M.p.: 252-254°C (dec.)

Example 46

20 3,4-Dimethoxy-N-[4-(2-fluoro-5-trifluoromethyl-phenyl)-
thiazol-2-yl]benzenesulphonamide

A mixture of 0.5 g of 4-(2-fluoro-5-trifluoromethyl-
phenyl)-thiazol-2-ylamine hydrobromide with 0.38 g of 3,4-
dimethoxy-benzenesulphonyl chloride was stirred overnight with
25 2 ml of pyridine. The resulting, red coloured suspension was
poured into 30 ml of 1N hydrochloric acid and the mixture was
extracted with ethyl acetate. The organic phase was dried with
magnesium sulphate and concentrated. The residue was dissolved
in a mixture of 20 ml of ethanol and 20 ml of 2N sodium
30 hydroxide solution. After the addition of 0.5 g of active charcoal
the mixture was stirred at room temperature for 30 minutes and
subsequently the active charcoal was filtered off. After
neutralization with concentrated hydrochloric acid the mixture
was concentrated and the residue was chromatographed on 40 g
35 of Kieselgel 60 with ethyl acetate/hexane (1:1) as the eluent. The
product-containing fractions were concentrated and, after
recrystallization from 15 ml of 50% ethanol, yielded 0.16 g of
N-[4-(3-fluoro-5-trifluoromethyl-phenyl)-thiazol-2-yl]-4-

methyl-benzenesulphonamide as colourless crystals.

M.p.: 123-125°C

5

Example 47

3-Bromo-4-methoxy-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzenesulphonamide

10 A mixture of 5.0 g of 4-(3-nitro-phenyl)-thiazol-2-ylamine hydrobromide with 5.2 g of 3-bromo-4-methoxy-benzene-sulphonyl chloride was stirred for 3 h with 20 ml of pyridine. The resulting, red coloured suspension was poured into 300 ml of 1N hydrochloric acid and the mixture was extracted with ethyl
15 acetate. The organic phase was dried with magnesium sulphate and concentrated. The residue was dissolved in a mixture of 300 ml of ethanol and 200 ml of 2N sodium hydroxide solution. After the addition of 4.5 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the
20 active charcoal was filtered off. 4.4 g of 3-bromo-4-methoxy-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzenesulphonamide separated as yellow crystals upon neutralization with concentrated hydrochloric acid.

25 M.p.: 200-202°C

Example 48

N-[4-(3-Hydroxy-4-methoxy-5-nitro-phenyl)-thiazol-2-yl]-4-methyl-benzenesulphonamide

30 50 mg of sodium hydride (60%) were added to a solution of 0.5 g of N-[4-(3,4-dihydroxy-5-nitro-phenyl)-thiazol-2-yl]-4-methyl-benzenesulphonamide in 5 ml of dimethylformamide. The
35 mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was dried with magnesium sulphate and concentrated. The residue was chromatographed on 60 g of

Kieselgel 60 with methylene chloride/acetone/formic acid (90:10:2.5) as the eluent. The product-containing fractions were concentrated and, after boiling with 20 ml of diethyl ether, yielded 0.17 g of N-[4-(3-hydroxy-4-methoxy-5-nitro-phenyl)-thiazol-2-yl]-4-methyl-benzenesulphonamide as orange coloured crystals.

M.p.: 210-212°C

10

Example 49

3,4-Dimethoxy-N-(4-naphthalen-1-yl-thiazol-2-yl)-benzenesulphonamide

15 A mixture of 10 g of 4-(1-naphthyl)-thiazol-2-ylamine hydrobromide with 8.5 g of 3,4-dimethoxy-benzenesulphonyl chloride was stirred for 18 hours with 30 ml of pyridine. The resulting, red coloured suspension was poured into 400 ml of 1N hydrochloric acid. The separated solid was dissolved in a mixture
20 of 400 ml of ethanol and 400 ml of 2N sodium hydroxide solution. After the addition of 8 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. After neutralization with concentrated hydrochloric acid the mixture was concentrated and the residue was taken up with ethyl acetate, dried
25 with magnesium sulphate and concentrated. Crystallization from 200 ml of ethyl acetate yielded 11.5 g of 3,4-dimethoxy-N-(4-naphthalen-1-yl-thiazol-2-yl)-benzenesulphonamide as colourless crystals.

30

M.p.: 132-133°C

Example 503,4-Dimethoxy-N-(4-naphthalen-2-yl-thiazol-2-yl)-benzene-sulphonamide

5

A mixture of 10 g of 4-(2-naphthyl)-thiazol-2-ylamine hydrobromide with 8.5 g of 3,4-dimethoxy-benzenesulphonyl chloride was stirred for 18 hours with 40 ml of pyridine. The resulting, red coloured suspension was poured into 400 ml of 1N hydrochloric acid and the mixture was extracted with ethyl acetate. The organic phase was dried with magnesium sulphate and (sic) concentrated. The residue was dissolved in a mixture of 500 ml of ethanol and 400 ml of 2N sodium hydroxide solution. After the addition of 10 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active charcoal was filtered off. 11.1 g of 3,4-dimethoxy-N-(4-naphthalen-2-yl-thiazol-2-yl)-benzenesulphonamide separated upon neutralization with concentrated hydrochloric acid in the form of colourless crystals, which were recrystallized from ethanol/water.

20

M.p.: 114-117°C.

Example 51

25

4-Methoxy-N-(4-naphthalen-1-yl-thiazol-2-yl)-benzene-sulphonamide

A mixture of 10 g of 4-(1-naphthyl)-thiazol-2-ylamine hydrobromide with 7.4 g of 4-methoxy-benzenesulphonyl chloride was stirred for 16 hours with 40 ml of pyridine. The resulting, red coloured suspension was poured into 400 ml of 1N hydrochloric acid and the extracted with ethyl acetate. The organic phases were combined, dried with magnesium sulphate and free from solvent. The residue was dissolved in a mixture of 500 ml of ethanol and 400 ml of 2N sodium hydroxide solution. After the addition of 10 g of active charcoal the mixture was stirred at room temperature for 30 minutes and subsequently the active

35

charcoal was filtered off. After neutralization with concentrated hydrochloric acid the mixture was concentrated, the residue was taken up with ethyl acetate, dried with magnesium sulphate and concentrated. Crystallization from ethyl acetate/hexane yielded
5 10.2 g of 4-methoxy-N-(4-naphthalen-1-yl-thiazol-2-yl)-benzenesulphonamide as colourless crystals, which were recrystallized once from ethyl acetate/hexane.

M.p.: 98-100°C

10

Intermediates

Example 52

15 3-(2-Amino-thiazol-4-yl)-benzonitrile

16.9 g of 3-bromoacetyl-benzonitrile were placed in 50 ml of methanol and treated at room temperature with 8 g of thiourea. The mixture was boiled for 2 1/2 hours and then cooled
20 to 0°C while stirring slowly. The product separated as the salt, was filtered off and converted into the base by the addition of 100 ml of 2N sodium hydroxide solution. The aqueous suspension was extracted with a total of 700 ml of methylene chloride and the organic phase was dried with magnesium sulphate. 9.6 g of 3-
25 (2-amino-thiazol-4-yl)-benzonitrile separated upon concentration.

M.p.: 195-198°C

30

Example 53

4-Cyclohexyl-benzenesulphonyl chloride

A solution of 10.6 ml of phenylcyclohexane in 100 ml of
35 methylene chloride was added at 5°C within 30 minutes to 13.8 ml of chlorosulphonic acid. The mixture was stirred at 5°C for 1 hour, poured into 400 ml of a 20% ammonium chloride solution and extracted twice with 300 ml of methylene chloride

each time. The organic phases were combined, dried with magnesium sulphate and the solvent was removed on a rotary evaporator. 13.6 g of 4-cyclohexyl-benzenesulphonyl chloride separated as a reddish oil, which was used without further
5 purification.

NMR (CDCl₃) ppm: 7.94 (d, 2H), 7.43 (d, 2H), 2.62 (m, 1H), 2.0-1.2 (m, 10 H)

10

Example 54

4-Isopropyl-benzenesulphonyl chloride

A solution of 11.6 ml of isopropylbenzene in 100 ml of
15 methylene chloride was added at 5°C within 30 minutes to 18.3 ml of chlorosulphonic acid. The reaction mixture was stirred at 5°C for 1 hour, poured on to 500 ml of ice-water and, after stirring for 5 minutes, treated with 100 g of ammonium chloride. After extraction with methylene chloride (1 x 800 ml,
20 1 x 500 ml) the organic phases were combined, dried with magnesium sulphate and the solvent was removed on a rotary evaporator. 12.3 g of 4-isopropyl-benzenesulphonyl chloride separated as a reddish oil, which was used without further purification.

25

NMR (CDCl₃) ppm: 7.96 (d, 2H), 7.46 (d, 2H), 3.04 (m, 1H), 1.30 (d, 6 H)

Example 55

30

4-(3-Trifluoromethyl-phenyl)-thiazol-2-ylamine hydrobromide

A solution of 8.1 g of 2-bromo-1-(3-trifluoromethyl-phenyl)-ethanone in 70 ml of methanol was treated at room
35 temperature with 3.2 g of thiourea and boiled for 1 hour. 4.1 g of 4-(3-trifluoromethyl-phenyl)-thiazol-2-ylamine hydrobromide separated as colourless crystals upon cooling to 0°C.

M.p.: 206-208°C

Example 56

5 4-(4-Benzyloxy-3-methoxy-phenyl)-thiazol-2-ylamine
hydrobromide

4-(4-Benzyloxy-3-methoxy-phenyl)-thiazol-2-yl-amine
hydrobromide was prepared in all respects analogously from 2-
10 bromo-1-(4-benzyloxy-3-methoxy-phenyl)-ethanone.

M.p.: 239-240°C

Example 57

15

4-(3,4-Bis-benzyloxy-phenyl)-thiazol-2-ylamine hydrobromide

4-(3,4-Bis-benzyloxy-phenyl)-thiazol-2-ylamine hydro-
bromide was prepared in all respects analogously from 2-bromo-
20 1-(3,4-bis-benzyloxy-phenyl)-ethanone.

M.p.: 166-167°C

Example 58

25

2-Bromo-1-(2-fluoro-5-trifluoromethyl-phenyl)-ethanone

A solution of 5.0 g of 2-fluoro-5-trifluoromethyl-aceto-
phenone in 35 ml of acetic acid was treated with 0.8 ml of
30 bromine at room temperature within 10 minutes. The brown
colour disappeared after stirring at room temperature for
3 hours. The reaction mixture was added to 150 ml of ice-water
and extracted twice with diethyl ether. The organic phases were
washed twice with saturated sodium bicarbonate solution,
35 combined, dried with sodium sulphate and concentrated. The
residue weighed 5.8 g, contained about 60% of 2-bromo-1-(2-
fluoro-5-trifluoromethyl-phenyl)-ethanone and was processed
without purification.

Example 59

5 4-(2-Fluoro-5-trifluoromethyl-phenyl)-thiazol-2-ylamine
hydrobromide

A solution of 5.8 g of 2-bromo-1-(2-fluoro-5-trifluoro-
methyl-phenyl)-ethanone in 44 ml of methanol was treated at
room temperature with 2.2 g of thiourea and boiled for 1 hour.
10 2.8 g of 4-(2-fluoro-5-trifluoromethyl-phenyl)-thiazol-2-
ylamine hydrobromide separated as colourless crystals upon
cooling to 0°C and after the addition of 15 ml of diethyl ether.

M.p.: 194-195°C

15

Example 60

2-Bromo-1-(3-fluoro-5-trifluoromethyl-phenyl)-ethanone

20 A solution of 5.8 g of 3-fluoro-5-trifluoromethyl-aceto-
phenone in 35 ml of acetic acid was treated with 0.94 ml of
bromine at room temperature within 10 minutes. The brown
colour disappeared after stirring at room temperature for
2 hours. The reaction mixture was added to 150 ml of ice-water
25 and extracted twice with diethyl ether. The organic phases were
washed twice with saturated sodium bicarbonate solution,
combined, dried with magnesium sulphate and concentrated. The
residue weighed 7.2 g, contained about 60% of 2-bromo-1-(3-
fluoro-5-trifluoromethyl-phenyl)-ethanone and was processed
30 without further purification.

Example 61

35 4-(3-Fluoro-5-trifluoromethyl-phenyl)-thiazol-2-ylamine
hydrobromide

A solution of 7.2 g of 2-bromo-1-(3-fluoro-5-trifluoro-
methyl-phenyl)-ethanone in 60 ml of methanol was treated at

room temperature with 2.7 g of thiourea and boiled for 1 hour. 5.2 g of 4-(3-fluoro-5-trifluoromethyl-phenyl)-thiazol-2-ylamine hydrobromide separated as colourless crystals upon cooling to 0°C and after the addition of 15 ml of diethyl ether.

5

M.p.: 219-221°C

Example 62

10 4-(2-Benzyloxy-phenyl)-thiazol-2-ylamine hydrobromide

A solution of 21.7 g of 2-bromo-1-(2-benzyloxy-phenyl)-ethanone in 150 ml of methanol was treated at room temperature with 7.6 g of thiourea and boiled for 1 hour. The reaction
15 mixture was concentrated to a volume of 60 ml. 20.7 g of 4-(2-benzyloxy-phenyl)-thiazol-2-ylamine hydrobromide separated as colourless crystals upon cooling to 0°C and after the addition of 250 ml of diethyl ether.

20 M.p.: 194-196°C

Example 63

4-(3-Benzyloxy-phenyl)-thiazol-2-ylamine hydrobromide

25

A solution of 22.5 g of 2-bromo-1-(3-benzyloxy-phenyl)-ethanone in 150 ml of methanol was treated at room temperature with 7.8 g of thiourea and boiled for 1 hour. 16.1 g of 4-(3-benzyloxy-phenyl)-thiazol-2-ylamine hydrobromide separated as
30 colourless crystals upon cooling to 0°C.

M.p.: 168-170°C

Example 64N-[4-(3-Bromo-phenyl)-thiazol-2-yl]-N-methoxymethyl-4-methyl-benzenesulphonamide

5

A solution of 0.72 g of N-[4-(3-bromo-phenyl)-thiazol-2-yl]-4-methyl-benzenesulphonamide and 0.6 ml of ethyldiisopropylamine in 10 ml of methylene chloride was cooled to 0°C and, after the addition of 0.13 ml of chloromethyl methyl ether, stirred at 0°C for 2 h. Thereafter, the mixture was treated with 40 ml of water and extracted with methylene chloride. The organic phase was dried with magnesium sulphate and concentrated. After chromatography on 60 g of Kieselgel 60 with ethyl acetate/hexane (1:3) as the eluent the product-containing fractions were concentrated. 0.64 g of colourless N-[4-(3-bromo-phenyl)-thiazol-2-yl]-N-methoxymethyl-4-methyl-benzenesulphonamide, obtained in amorphous form, was processed without further purification.

20 NMR (CDCl₃) ppm: 7.89 (s, 1H), 7.85 (d, 2H), 7.56 (d, 1H), 7.38 (d, 1H) 7.31 (d, 2H), 7.23 (dd, 1H), 7.18 (s, 1H), 5.51 (s, 2H), 3.47 (s, 3H), 2.42 (s, 3H).

Example 65

25

N-(4-Biphenyl-3-yl-thiazol-2-yl)-N-methoxymethyl-4-methyl-benzenesulphonamide

A solution of 0.5 g of N-[4-(3-bromo-phenyl)-thiazol-2-yl]-N-methoxymethyl-4-methyl-benzenesulphonamide in 8 ml of toluene was treated in succession with 0.1 g of anhydrous lithium chloride, 60 mg of tetrakis(triphenylphosphine)-palladium, 0.23 g of phenylboric acid and 2 ml of 2N potassium carbonate solution. The mixture was boiled overnight, cooled and, after the addition of water, extracted with ethyl acetate. The organic phases were combined, dried with magnesium sulphate and concentrated. The residue was chromatographed on 80 g of Kieselgel 60 with ethyl acetate/hexane (1:4) as the eluent. The

product-containing fractions were concentrated and yielded 0.29 g of colourless, amorphous N-(4-biphenyl-3-yl-thiazol-2-yl)-N-methoxymethyl-4-methyl-benzenesulphonamide, which was processed without further purification.

5

NMR (CDCl₃) ppm: 7.99 (s, 1H), 7.86 (d, 2H), 7.72 (d, 1H), 7.6- 7.2 (m, 9H), 6.80 (d, 1H), 5.53 (s, 2H), 3.48 (s, 3H), 2.38 (s, 3H).

Example A

10

Tablets of the following composition are produced in the usual manner:

	<u>mg/tablet</u>
15 White corn starch	100
Powd. Lactose	95
White corn starch	35
Polyvinylpyrrolidone	8
20 Na carboxymethylstarch	10
Magnesium stearate	<u>2</u>
Tablet weight	250

Example B

25

Tablets of the following composition are produced in the usual manner:

	<u>mg/tablet</u>
30 White corn starch	200
Powd. Lactose	100
White corn starch	64
Polyvinylpyrrolidone	12
Na carboxymethylstarch	20
35 Magnesium stearate	<u>4</u>
Tablet weight	400

Example C

Capsules of the following composition are produced:

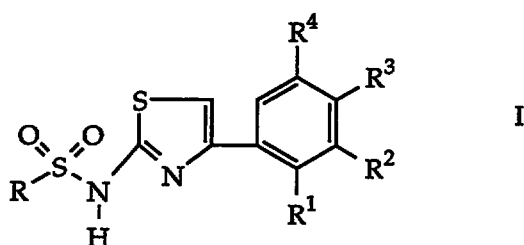
5		<u>mg/capsule</u>
	White corn starch	50
	Cryst. lactose	60
	Microcrystalline cellulose	34
	Talc	5
10	Magnesium stearate	<u>1</u>
	Capsule fill weight	150

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



Claims

1. The use of compounds of the general formula



wherein

10 R signifies lower-alkyl, phenyl, benzyl, naphthyl, pyridyl or thienyl, optionally substituted by one or more lower-alkyl, lower-alkoxy, lower-alkyl-carbonyl-amino, halogen, cycloalkyl, nitro, amino, methylenedioxy, phenoxy or benzyloxy substituents, and the aromatic rings, can, in

15 turn, be substituted by nitro, halogen or amino,

20 R¹-R⁴ signify hydrogen, halogen, hydroxy, lower-alkyl, nitro, cyano, amino, lower-alkoxy, benzyloxy, trifluoromethyl or phenyl, optionally substituted by one or more lower-alkyl, trifluoromethyl, nitro, amino or hydroxy substituents, and wherein R¹ and R² or R² and R³ together can form a benzene ring which optionally can be substituted by halogen, trifluoromethyl, nitro, lower-alkyl

25 or lower-alkoxy,

and of their pharmaceutically acceptable salts as kynurenin-3-hydroxylase inhibitors in the control or prevention of neuro-degenerative disorders, neurological disorders resulting from an

30 activation of the immune system or psychiatric illnesses and, respectively, for the production of corresponding medicaments.

2. The use in accordance with claim 1 of compounds of formula I defined in claim 1 in which R signifies 4-methoxy-





phenyl, 4-methylphenyl, 4-aminophenyl, 3,4-dimethoxyphenyl or 2-naphthyl and R^1 - R^4 signify hydrogen, fluorine, nitro or trifluoromethyl or R^2 and R^3 together form a benzene ring.

5 3. The use in accordance with claim 1 of

4-methoxy-N-(4-naphthalen-2-yl-thiazol-2-yl)-benzene-sulphonamide,

4-amino-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzene-
10 sulphonamide,

4-methyl-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzene-sulphonamide,

3,4-dimethoxy-N-[4-(3-nitro-phenyl)thiazol-2-yl]-benzenesulphonamide,

15 4-methoxy-N-[4-(3-nitro-phenyl)-thiazol-2-yl]-benzene-sulphonamide,

naphthalene-2-sulphonic acid [4-(3-nitro-phenyl)-thiazol-2-yl]-amide,

N-[4-(2-fluoro-5-trifluoromethyl-phenyl)-thiazol-2-yl]-4-
20 methyl-benzenesulphonamide,

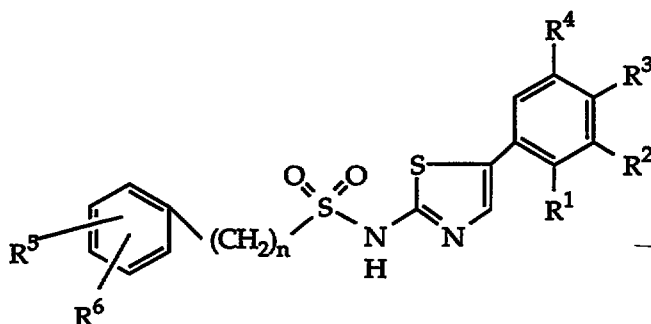
N-[4-(3-fluoro-5-trifluoromethyl-phenyl)-thiazol-2-yl]-4-methyl-benzenesulphonamide,

4-methyl-N-[4-(4-nitro-phenyl)-thiazol-2-yl]-benzene-sulphonamide,

25 4-amino-N-[4-(2-fluoro-5-trifluoromethyl-phenyl)-thiazol-2-yl]-benzenesulphonamide and

3,4-dimethoxy-N-[4-(2-fluoro-5-trifluoromethyl-phenyl)-thiazol-2-yl]-benzenesulphonamide.

30 4. Novel compounds from the group of compounds of general formula I from claim 1



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wherein

R¹-R⁴ have the significances given in claim 1,

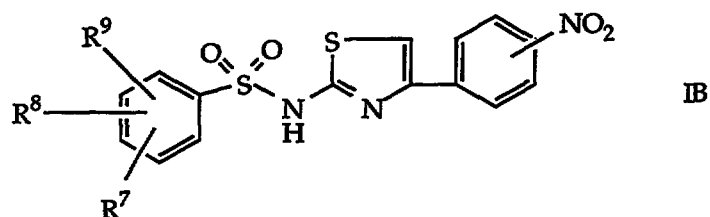
R⁵ signifies hydrogen or lower-alkyl,

5 R⁶ signifies hydrogen, lower-alkyl, lower alkoxy, cycloalkyl or benzyl and

n signifies 0 or 1 and

in which R⁵ and R⁶ together can form a methylenedioxy group, with the proviso that R⁵ and R⁶ can not
10 simultaneously be hydrogen.

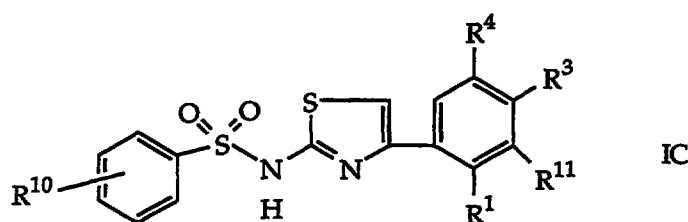
5. Novel compounds from the group of compounds of general formula I from claim 1



wherein R⁷-R⁹ signify hydrogen, halogen, lower-alkoxy or 4-NO₂-phenoxy, with the proviso that at least one of R⁷-R⁹ is halogen.

20

6. Novel compounds from the group of compounds of general formula I from claim 1



wherein

R¹⁰ signifies amino or -NHCOR¹²,

R¹² signifies lower alkyl,

R¹, R³ and R⁴ have the significances given in claim 1 and

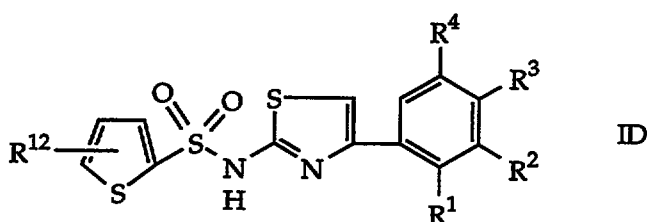
30 R¹¹ signifies hydrogen, hydroxy, nitro, cyano, amino,





trifluoromethyl, benzyloxy or phenyl, optionally substituted by one or more lower-alkyl, trifluoromethyl, nitro, amino or hydroxy substituents, and R¹¹ and R³ together can form a phenyl ring.

7. Novel compounds from the group of compounds of general formula I from claim 1

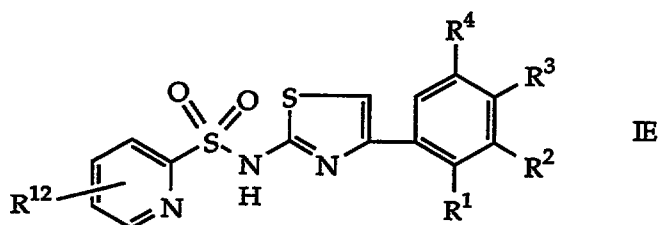


wherein

R¹-R⁴ have the significances given in claim 1 and

R¹² has the significance given in claim 6.

8. Novel compounds from the group of compounds of general formula I from claim 1



wherein

R¹-R⁴ have the significances given in claim 1 and

R¹² has the significance given in claim 6.

9. A medicament containing one or more compounds according to any one of claims 4-8 and a therapeutically inert excipient.





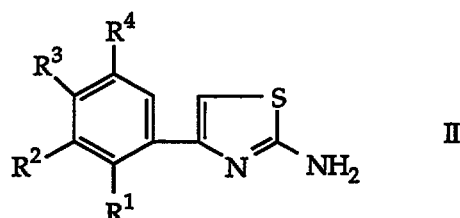
10. A medicament according to claim 9, especially for the control of illnesses or conditions which are associated with a malfunction of the glutamatergic neurotransmission and/or which lead to an excessive production of quinolinic acid, such as
5 neurodegenerative disorders (Huntington's chorea, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, epilepsy), consequences of stroke and/or cerebral ischaemia, hypoxia, multi-infarct dementia, consequences of cerebral trauma or damage as well as trauma and damage to the spinal cord,
10 neurological disorders resulting from an activation of the immune system (e.g. AIDS-dementia complex, infections such as e.g. viral or bacterial meningitis and cancers with cerebral localization), autoimmune diseases (multiple sclerosis) as well as psychiatric illnesses (schizophrenia, chronic anxiety).

15

11. A process for the manufacture of compounds according to any one of claims 4-8, which process comprises

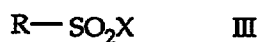
a) reacting a compound of the general formula

20



with a suitable sulphonyl halide of the general formula

25



wherein R and R¹-R⁴ have the significances given in claim 1 and X signifies halogen,

or

30

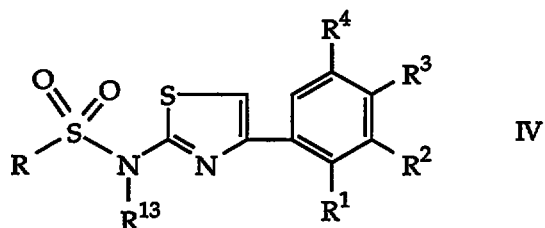
b) cleaving off the protecting group from a compound of the general formula

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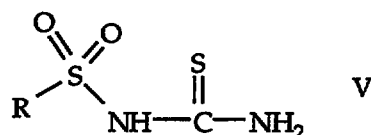
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wherein R and R¹-R⁴ have the significances given in claim 1
and R¹³ signifies a sulphonamide protecting group,

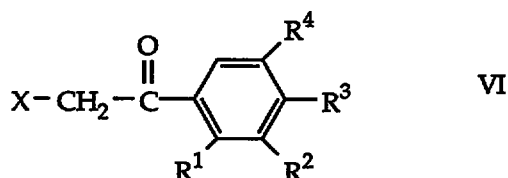
5 or

c) reacting a compound of the general formula



10

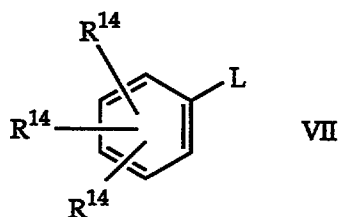
wherein R has the significance given in claim 1,
with an appropriate compound of the general formula



15

wherein R¹-R⁴ have the significances given in claim 1
and X has the significance given earlier in this claim,
to give a thiazole derivative of formula I, or

20 d) reacting an appropriate compound of formula IV in
which R² or R⁴ signifies bromine or iodine and R¹ and/or R⁴
are/is different from bromine or iodine with a compound of the
general formula



25



wherein L signifies a suitable leaving group and R^{14} are the same or different and signify lower-alkyl, lower-alkoxy, trifluoromethyl, nitro, amino or hydroxy,

or

5

e) hydrolyzing a compound of general formula I in which R signifies phenyl substituted by lower-alkyl-carbonyl-amino and R^1 - R^4 have the significances given in claim 1 to a compound of general formula I in which R signifies phenyl substituted by

10 amino, and

f) if desired, converting a compound of general formula I into a pharmaceutically acceptable salt.

15 12. Compounds according to any one of claims 4-8, insofar as they are manufactured by the process according to claim 11 or a process equivalent thereto.

13. Compounds according to any one of claims 4-8 for use
20 as therapeutically active substances, especially for the control or prevention of neurodegenerative disorders (Huntington's chorea, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, epilepsy), consequences of stroke and/or cerebral ischaemia, hypoxia, multi-infarct dementia, consequences of
25 cerebral trauma or damage as well as trauma and damage to the spinal cord, neurological disorders resulting from an activation of the immune system (e.g. AIDS-dementia complex, infections such as e.g. viral or bacterial meningitis and cancers with cerebral localization), autoimmune diseases (multiple sclerosis) as well
30 as psychiatric illnesses (schizophrenia, chronic anxiety).

14. The use of compounds according to any one of claims 4-8 as therapeutically active substances.

35 15. The use of compounds according to any one of claims 4-8 for the control or prevention of neurodegenerative disorders (Huntington's chorea, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, epilepsy), consequences of stroke

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and/or cerebral ischaemia, hypoxia, multi-infarct dementia,
consequences of cerebral trauma or damage as well as trauma and
damage to the spinal cord, neurological disorders resulting from
an activation of the immune system (e.g. AIDS-dementia complex,
5 infections such as e.g. viral or bacterial meningitis and cancers
with cerebral localization), autoimmune diseases (multiple
sclerosis) as well as psychiatric illness (schizophrenia, chronic
anxiety) and, respectively, for the production of corresponding
medicaments.

10

16. The invention as hereinbefore described.

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