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54	TITLE OF INVENTION

Tetrahydro-(benzo or thieno)-azepine-pyrazine and triazine derivatives as mGluR 1 antagonists

57	ABSTRACT (NOT MORE THAN 150 WORDS)

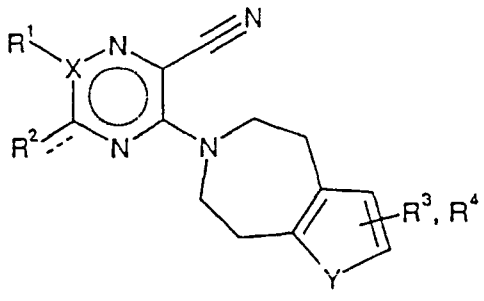
NUMBER OF SHEETS 45

The sheet(s) containing the abstract is/are attached.

If no classification is furnished, Form P.9 should accompany this form.
The figure of the drawing to which the abstract refers is attached.

A&A P208

(54) Title: TETRAHYDRO-(BENZO OR THIENO)-AZEPINE-PYRAZINE AND TRIAZINE DERIVATIVES AS MGLUR 1 ANTAGONISTS

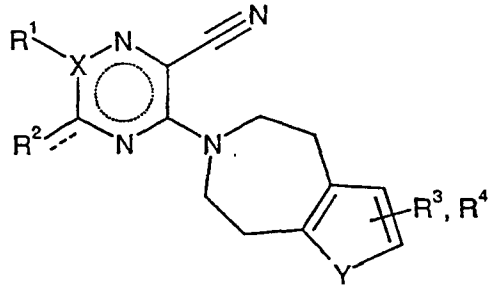


(I)

(57) Abstract: The invention relates to compounds which are represented by general formula (I) wherein R^1, R^2, R^3 R^4, X and Y are as defined in the specification, as well as pharmaceutically acceptable salts thereof. The invention further relates to medicaments containing these compounds and to a process for their preparation. The compounds possess affinity towards metabotropic glutamate receptors and are therefore useful in the treatment or prevention of acute and/or chronic neurological disorders.

Tetrahydro-(benzo or thieno)-azepine- pyrazine and triazine derivatives as mGluR 1 antagonists

The present invention relates to 1,2,4,5-tetrahydro-benzo[d]azepine- pyrazine and triazine derivatives and 1,2,4,5-tetrahydro-thieno[d]azepine- pyrazine and triazine derivatives of the general formula



I

wherein

R^1 signifies hydrogen, lower alkyl, lower alkenyl, or unsubstituted phenyl or phenyl substituted in meta or para position with one or more substituents selected from the group consisting of lower alkyl, lower alkoxy or halogen, or is absent, if X is –N= or =N-;

R^2 signifies hydrogen, lower alkyl, lower alkenyl, =O, -S-lower alkyl, $-SO_2$-lower alkyl or -OR, $-O(CHR)_{m+1}-OR$, $-NR_2$, $-NH-NR_2$, $-N(R)(CHR)_{m+1}-OR$, $-N(R)(CHR)_m$-pyridino, $-N(R)(CHR)_n-(C_3-C_6)$cycloalkyl, $-N(R)(CHR)_m(CR_2)-NR_2$, or $-N(R)(CHR)_{m+1}-NH-C(O)-O$-lower alkyl;

m is 1, 2, 3, 4, 5 or 6;

n is 0, 1, 2, 3, 4 or 5;

R signifies hydrogen, lower alkyl or lower alkenyl, independently from each other, if more than one R is present;

X signifies –N=, =N-, >C= or =C<; and

the dotted line may be a bond,

Y signifies -CH=CH-, -CH=CR^3-, -CR^3=CH-, -CR^3=CR^4- or S; and

R^3, R^4 signify independently from each other hydrogen, lower alkyl, lower alkoxy or halogen with the proviso, that if Y represents a vinylene group, only one group R^3 and one group R^4 may be present in the entire benzene ring;

as well as their pharmaceutically acceptable salts in their racemic and optically active form.

It has surprisingly been found that the compounds of general formula I are antagonists at metabotropic glutamate receptors.

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

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

At present, eight different members of these mGluRs are known and of these some even have sub-types. On the basis of structural parameters, the different second messenger signaling pathways and the different affinity to low-molecular weight chemical compounds, these eight receptors can be sub-divided into three sub-groups:

mGluR1 and mGluR5 belong to group I, mGluR2 and mGluR3 belong to group II and mGluR4, mGluR6, mGluR7 and mGluR8 belong to group III.

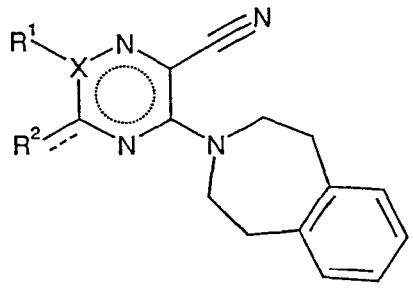
Ligands of metabotropic glutamate receptors belonging to the first group can be used for the treatment or prevention of acute and/or chronic neurological disorders such as epilepsy, stroke, chronic and acute pain, psychosis, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits.

Other treatable indications in this connection are restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia. Further treatable indications are Huntington's chorea, amyotrophic lateral sclerosis (ALS), dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficiency functions, such as

e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, opiate addiction, anxiety, vomiting, dyskinesia and depression.

Objects of the present invention are compounds of formula I and pharmaceutically acceptable salts thereof and their use as pharmaceutically active substances. Methods for the preparation of the above mentioned substances and medicaments based on compounds in accordance with the invention and their production are also objects of the present invention as well as the use of the compounds in accordance with the invention in the control or prevention of illnesses of the aforementioned kind, and, respectively, for the production of corresponding medicaments.

Preferred compounds of formula I within the scope of the present invention are those having the general formula



I-A

wherein

R^1 signifies hydrogen, lower alkyl, lower alkenyl, or unsubstituted phenyl or phenyl substituted in meta or para positions with one or more substituents selected from the group consisting of lower alkyl, lower alkoxy or halogen,
or is absent, if X is –N= or =N-;

R^2 signifies hydrogen, lower alkyl, lower alkenyl, =O, -S-lower alkyl,
$-SO_2$-lower alkyl or
-OR, $-O(CHR)_{m+1}-OR$, $-NR_2$, $-NH-NR_2$, $-N(R)(CHR)_{m+1}-OR$,
$-N(R)(CHR)_m$-pyridino, $-N(R)(CHR)_n-(C_3-C_6)$cycloalkyl,
$-N(R)(CHR)_m(CR_2)-NR_2$, or $-N(R)(CHR)_{m+1}-NH-C(O)-O$-lower alkyl;

m is 1, 2, 3, 4, 5 or 6;

n is 0, 1, 2, 3, 4 or 5;

R signifies hydrogen, lower alkyl or lower alkenyl, independently from each other, if more than one R is present;

X signifies –N=, =N-, >C= or =C<; and

the dotted line may be a bond,

as well as their pharmaceutically acceptable salts in their racemic and optically active form.

Preferred compounds of formula I-A within the scope of the present invention are those, in which
R^1 is absent and X is –N= or =N–; and
R^2 is $-NR_2$, $-NH-NR_2$, $-N(R)(CHR)_{m+1}OR$, $-N(R)(CHR)_m$-pyridino, $-N(R)(CHR)_n-(C_3-C_6)$cycloalkyl, $-N(R)(CHR)_m(CR_2)-NR_2$, or $-N(R)(CHR)_{m+1}$-NH-C(O)-O-lower alkyl.

The following are examples of such compounds:
3-Amino-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile,
3-(cyclopropylmethyl-amino)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile,
3-(2-hydroxy-ethylamino)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile,
(RS)-3-(2-hydroxy-propylamino)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile,
3-hydrazino-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile,
{2-[6-cyano-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazin-3-ylamino]-ethyl}-carbamic acid tert-butyl ester, or
3-(2-pyridin-3-yl-ethylamino)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile.

Especially preferred are those compounds of formula I-A, in which
R^1 is absent and X is –N= or =N–; and
R^2 signifies $-N(R)(CHR)_{m+1}$-OR, $-N(R)(CHR)_m$-pyridino or $-N(R)(CHR)_n-(C_3-C_6)$-cycloalkyl.

Examples of such compounds are the following:
3-(cyclopropylmethyl-amino)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile,
3-(2-hydroxy-ethylamino)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile,

(RS)-3-(2-hydroxy-propylamino)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile, or
3-(2-pyridin-3-yl-ethylamino)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile.

Compounds of formula I, in which
X signifies >C= or =C< and R^1 and R^2 are lower alkyl,
are also preferred.

The following are examples of such compounds:
5-ethyl-6-methyl-3-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-pyrazine-2-carbonitrile, or
6-ethyl-5-methyl-3-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-pyrazine-2-carbonitrile.

Especially preferred are such compounds of formula I, in which
X signifies >C= or =C< and R^1 signifies ethyl.

6-Ethyl-5-methyl-3-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-pyrazine-2-carbonitrile is an example of such a compound.

Also preferred are compounds of formula I, in which
X signifies >C= or =C< and R^1 signifies unsubstituted phenyl or phenyl substituted in meta or para positions with one or more substituents selected from the group consisting of lower alkyl, lower alkoxy or halogen.

An example of such a compound is 5-methyl-6-phenyl-3-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-pyrazine-2-carbonitrile.

Further preferred compounds are those, in which
X signifies >C= or =C< and R^2 signifies $-N(R)(CHR)_{m+1}-OR$ with R signifying independently from each other hydrogen, lower alkyl or lower alkenyl.

5-(2-hydroxy-ethylamino)-3-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-pyrazine-2-carbonitrile is an example of such a compound.

The term "lower alkyl" used in the present description denotes straight-chain or branched saturated hydrocarbon residues with 1-7 carbon atoms, preferably with 1-4 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl and the like.

The term "lower alkenyl" used in the present description denotes straight-chain or branched unsaturated hydrocarbon residues with 2-7 carbon atoms, preferably with 2-4 carbon atoms.

The term "lower alkoxy" denotes a lower alkyl group as defined above linked to an oxygen group. Preferred alkoxy groups are methoxy or ethoxy.

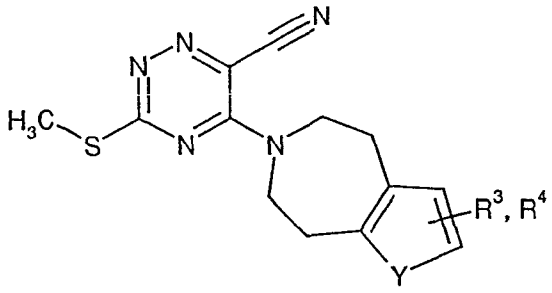
The term "cycloalkyl" denotes a saturated carbocyclic group containing from 3 to 6 carbon atoms, preferred are cyclopropyl, cyclopentyl or cyclohexyl.

The term "halogen" embraces fluorine, chlorine, bromine and iodine.

The term "phenyl substituted in meta or para position with one or more substituents selected from the group consisting of lower alkyl, lower alkoxy or halogen" means the homocyclic six membered aromatic ring which may be substituted by one or more substituents selected from the group consisting of lower alkyl, lower alkoxy or halogen in the para and/or meta positions, relative to the ring carbon that is attached to one of the carbons of the pyrazine ring of the compounds of formula I.

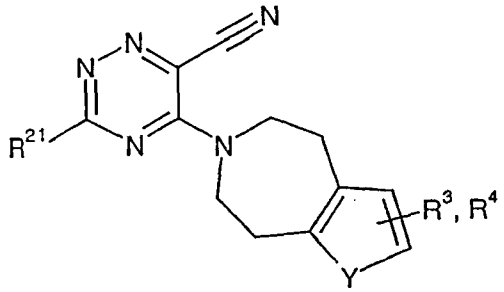
The compounds of general formula I and their pharmaceutically acceptable salts can be manufactured by

a) reacting the compound of the formula



I-2

with nucleophiles to obtain a compound of formula



I-1

wherein R^{21} signifies -OR, -O(CHR)$_{m+1}$-OR, -NR$_2$, -NH-NR$_2$, -N(R)(CHR)$_{m+1}$-OR, -N(R)(CHR)$_m$-pyridino, -N(R)(CHR)$_n$-(C$_3$-C$_6$)cycloalkyl, -N(R)(CHR)$_m$(CR$_2$)-NR$_2$, or -N(R)(CHR)$_{m+1}$-NH-C(O)-O-lower alkyl as defined before,

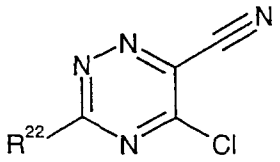
and, if desired,

converting a functional group of R^{21} in a compound of formula I-1 into another functional group to obtain another compound of formula I-1,

and, if desired,

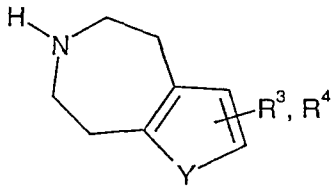
converting a compound of formula I-1 into a pharmaceutically acceptable salt; or

b) reacting a compound of the formula



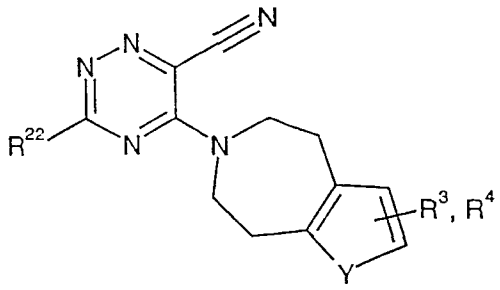
II-1

wherein R^{22} signifies alkyl, with the compound of formula



III

to obtain a compound of formula

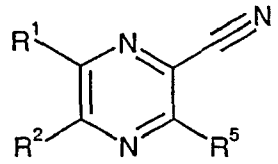


I-3

and, if desired,

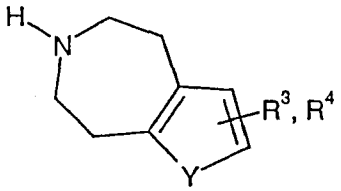
converting a compound of formula I-3 into a pharmaceutically acceptable salt; or

c) reacting a compound of the formula



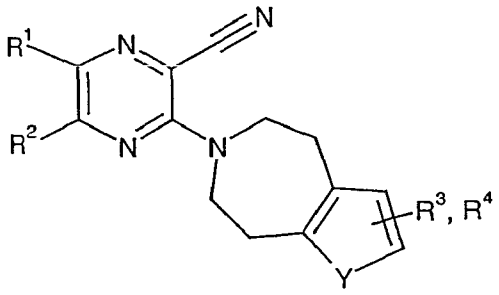
II-2

wherein R^5 signifies halogen, with the compound of formula



III

to obtain a compound of formula



I-4

and, if desired,

converting a functional group of R^2 in a compound of formula I-4 into another functional group to obtain another compound of formula I-4,

and, if desired,

converting a compound of formula I-4 into a pharmaceutically acceptable salt.

3-Methylsulfanyl-5-(1,2,4,5-tetrahydro-benzo- or thieno-azepin-3-yl)-[1,2,4]triazine-6-carbonitriles (I-2) are prepared by reaction of 3-(methylthio)-5-chloro-6-

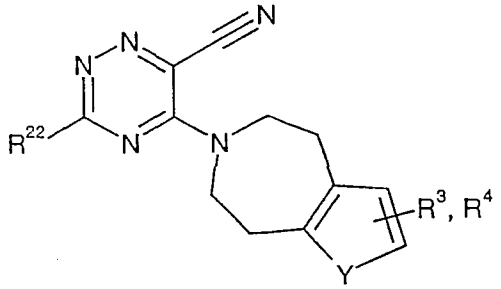
cyano-1,2,4-triazine (J.J.Huang, *J. Org. Chem.* 1985, 50, 2293-2298) with tetrahydro-benzo- or thieno-azepine compounds III, e.g. 2,3,4,5-tetrahydro-1H-benzo[d]azepine hydrochloride (*J. Heterocycl. Chem.* 1971, 8(5), 779-83), in the presence of a base like triethylamine or ethyl-diisopropylamine in solvents like N,N-dimethylformamide, dimethylsulfoxide, methyl-ethylketone, ethanol, dioxane or tetrahydrofuran at temperatures between 10 and 50 °C.

Substitution of the Me-S-group in compound I-2 by optionally substituted N-nucleophiles can be performed in water, ethanol, N,N-dimethylformamide, dimethylsulfoxide, 1,2-dimethoxyethane, preferentially in dioxane at elevated temperatures, preferentially 100 °C to 160 °C.

Substitution of the Me-S-group in compound I-2 by optionally substituted O-nucleophiles can be performed in an inert solvent as ethers, like 1,2-dimethoxyethane or dioxane at temperatures between room temperature and 120 °C after transformation of the corresponding alcohol into an alcoholate using a base like sodium hydride or potassium hydride.

The functionalization of the O- and N-nucleophiles can also serve as a protective function. Thus, modifications at the other part of the R^{21}-substituent are allowed, e.g. removal of a N-protecting group, like the tert-butoxycarbonyl group, by methods well documented in the literature.

Compounds of general formula I-1 can also be prepared by oxidation of the thioether I-2 to the corresponding sulfon according to known oxidative methods, e.g. by 3-chloroperbenzoic acid in dichloromethane, followed by treatment with thiolates, alcoholates, amines or aqueous base, e.g. like sodium carbonate or sodium hydrogencarbonate, thus yielding the group R^{21}.



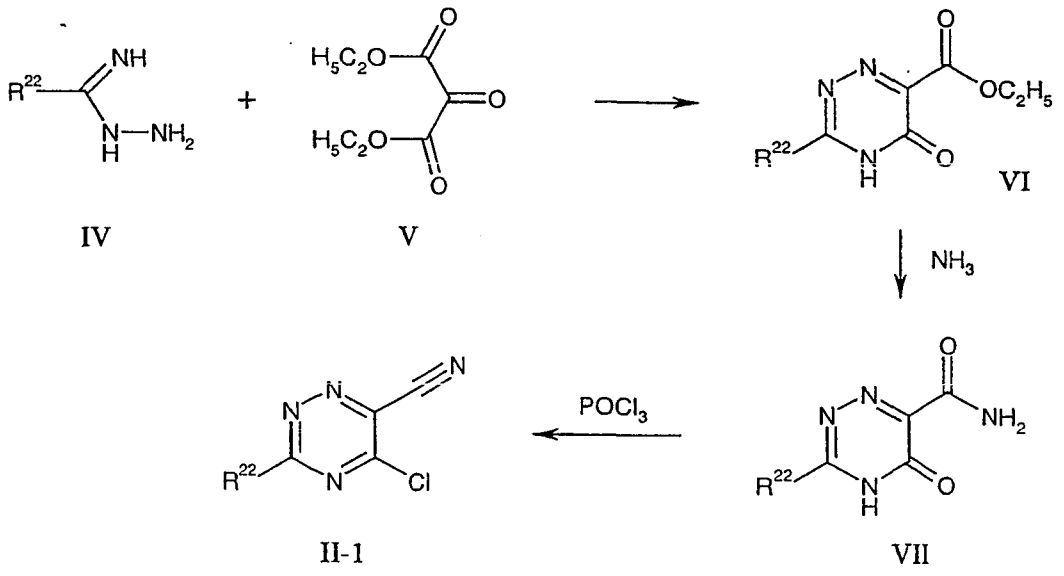
I-3

Compounds of general formula I-3 wherein R^{22} signifies lower alkyl can be prepared by reacting the intermediate II-1 with tetrahydro-benzo- or thieno-azepine compounds III,

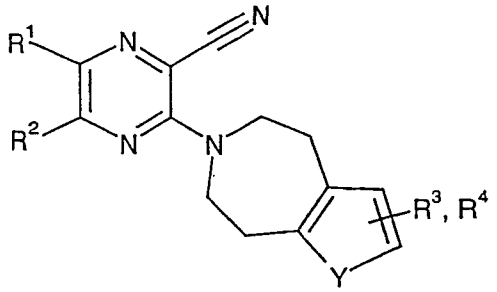
e.g. 2,3,4,5-tetrahydro-1H-benzo[d]azepine hydrochloride (*J. Heterocycl. Chem.* 1971, 8(5), 779-83), in the presence of a base like triethylamine or ethyl-diisopropylamine in solvents like N,N-dimethylformamide, dimethylsulfoxide, methyl-ethylketone, ethanol, dioxane or tetrahydrofuran at temperatures between 10 and 50 °C.

The intermediate II-1 can be synthesized in analogy to the procedure as described in *J.Org.Chem.* 1972, 37 (24), 3958-3960, starting with the condensation of the corresponding amidrazones IV and methyl or ethyl oxomalonate V, followed by ammonolysis of the ester VI, and, finally, dehydration of the amide VII and substitution of the hydroxy group by chlorine (scheme 1).

Scheme 1



Compounds of general formula

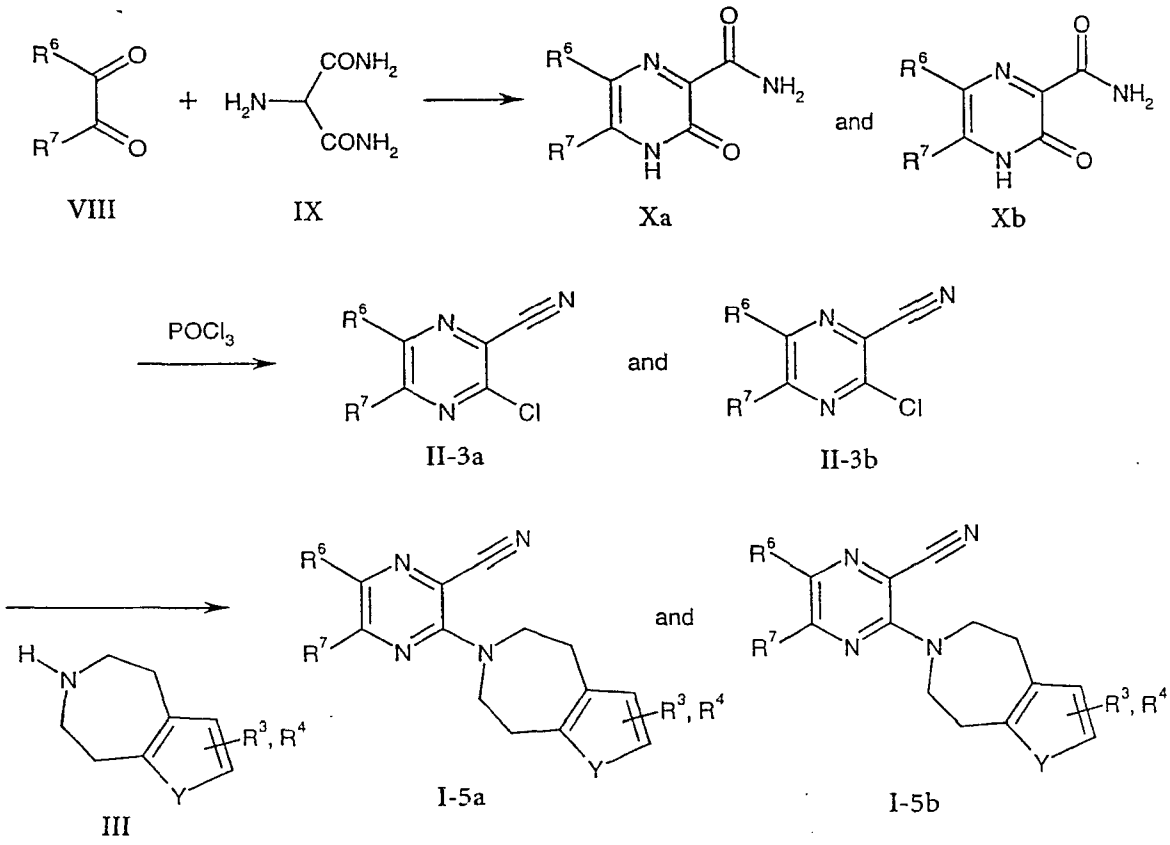


I-4

are prepared by methods as shown in schemes 2, 3 and 4 and described in the following.

1,2-Dicarbonyl compounds VIII with R^6 and R^7 signifying both independently from each other hydrogen, optionally substituted phenyl, lower alkyl or lower alkenyl, react with 2-amino-malonic acid diamide IX as described in *J. Amer. Chem. Soc.* 1949, 71, 78-81, either in the presence of an aqueous base at temperatures between 0 °C and 60 °C or in the absence of a base in solvents like water or an alcohol at temperatures between room temperature and 120 °C to form the two 3-oxo-3,4-dihydro-pyrazine-2-carboxylic acid amides Xa and Xb. Treatment of Xa and Xb either separately or as a mixture with phosphorus oxychloride and optionally additional phosphorus pentachloride in the presence of triethylamine or diethylaniline at temperatures between 40 °C and 120 °C give 3-chloro-pyrazine-2-carbonitriles II-3a and II-3b (scheme 2).

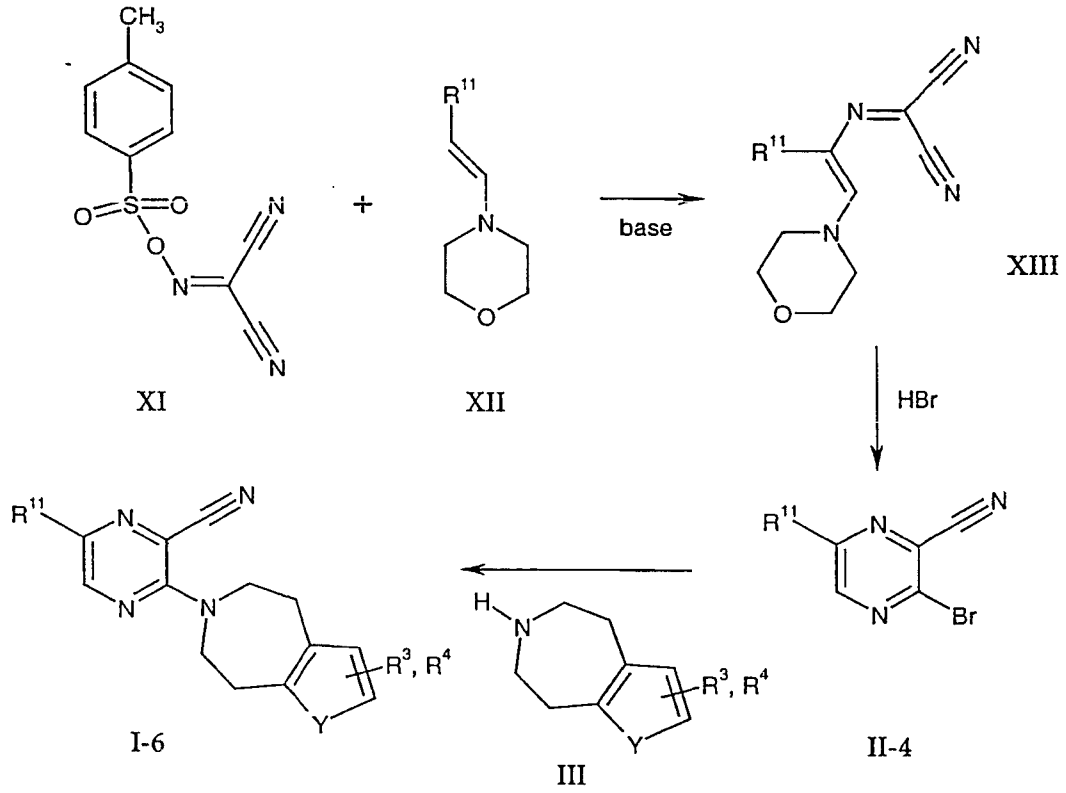
Scheme 2



3-Chloro-pyrazine-2-carbonitriles II-3a and II-3b react either separately or as a mixture with tetrahydro-benzo- or thieno-azepine compounds III or their hydrochlorides in solvents like N,N-dimethylformamide, acetonitrile, acetone or dimethylsulfoxide in the presence of a base like potassium carbonate or a tertiary amine as diisopropyl-ethylamine at temperatures between room temperature and 80 °C to form the desired 3-(tetrahydro-benzo- or thieno-azepine-3-yl)-pyrazine-2-carbonitriles I-5a and I-5b, which can be separated by known methods such as chromatography or crystallization.

In an alternative method (scheme 3), bromopyrazine derivatives of formula II-4 are prepared by reacting O-tosylisonitrosomalononitrile XI with morpholino-enamines of formula XII with R^{11} signifying lower alkyl or lower alkenyl, in the presence of a base like pyridine, triethylamine or diisopropyl-ethylamine in aprotic solvents like ether, tetraydrofuran or N,N-dimethylformamide at temperatures between –20 °C and 60 °C to obtain (morpholino-alkenylimino)malononitriles XIII (*Helv. Chim. Acta* 1986, 49, 793-802). Treatment of the (morpholino-alkenylimino)malononitriles XIII with hydrobromic acid in acetic acid between room temperature and 80 °C induces a cyclisation reaction leading to the bromo-pyrazines II-4 (*Helv. Chim.Acta* 1990, 73, 1210-1214).

Scheme 3

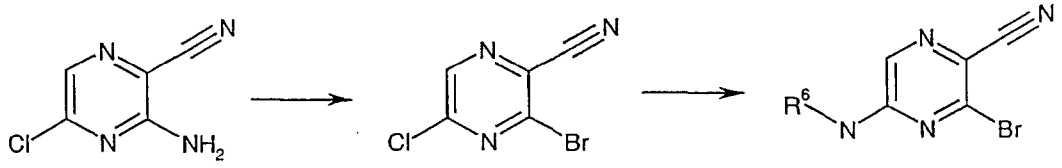


Bromo-pyrazines II-4 react with tetrahydro-benzo or thieno-azepine compounds III or their hydrochlorides in solvents like N,N-dimethylformamide, acetonitrile, acetone or dimethylsulfoxide in the presence of a base like potassium carbonate or a tertiary amine like diisopropyl-ethylamine at temperatures between room temperature and 80 °C to form the desired 3-(tetrahydro-benzo- or thieno-azepine-3-yl)-pyrazine-2-carbonitriles I-6.

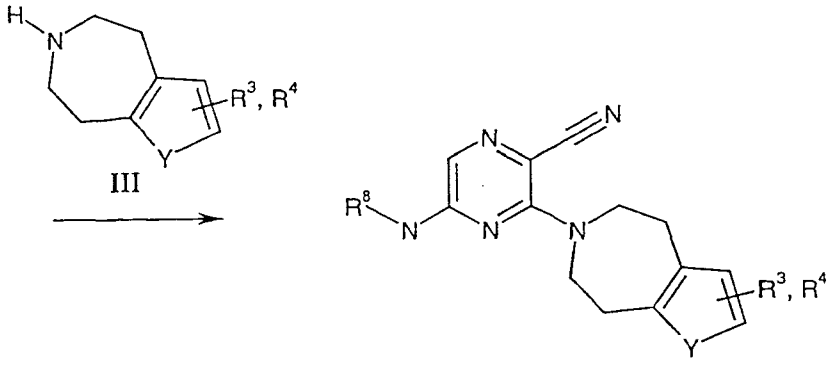
3-(Tetrahydro-benzo- or thieno-azepine-3-yl)-pyrazine-2-carbonitriles of formula I-7 can be prepared according to scheme 4.

Diazotization of the 3-amino-5-chloro-2-cyano-pyrazine XIV (*J.Org.Chem.* 1975, 40, 2341-2347) with t-butyl-nitrite in solvents like acetonitrile or N,N-dimethylformamide in the presence of copper-(II)-bromide at temperatures between room temperature and 95 °C gives the 3-bromo-5-chloro-2-cyano-pyrazine II-5. The 3-bromo-5-chloro-2-cyano-pyrazine II-5 reacts with one equivalent of a primary or secondary amine to two products, in which either the chloro-atom or the bromo-atom is replaced in the amine moiety. If the reaction is performed with a primary amine R^8NH_2 in a solvent like dioxane or tetrahydrofuran in the presence of a base like triethylamine or diisopropylethylamine, preferentially at room temperature, then compound II-6 with replaced chloro-atom can be obtained with reasonable selectivity. In a second analogous reaction, tetrahydro-benzo- or thieno-azepine compounds III or their hydrochlorides can then be reacted with II-6 in solvents like N,N-dimethylformamide, tetrahydrofuran, dioxane, acetonitrile, acetone or dimethylsulfoxide and in the presence of a base like potassium carbonate or a tertiary amine like diisopropyl-ethylamine at temperatures between room temperature and 80 °C giving compounds I-7.

Scheme 4



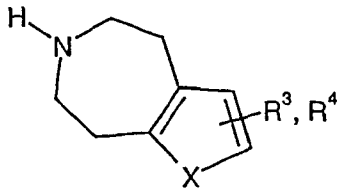
XIV II-5 II-6



III

I-7

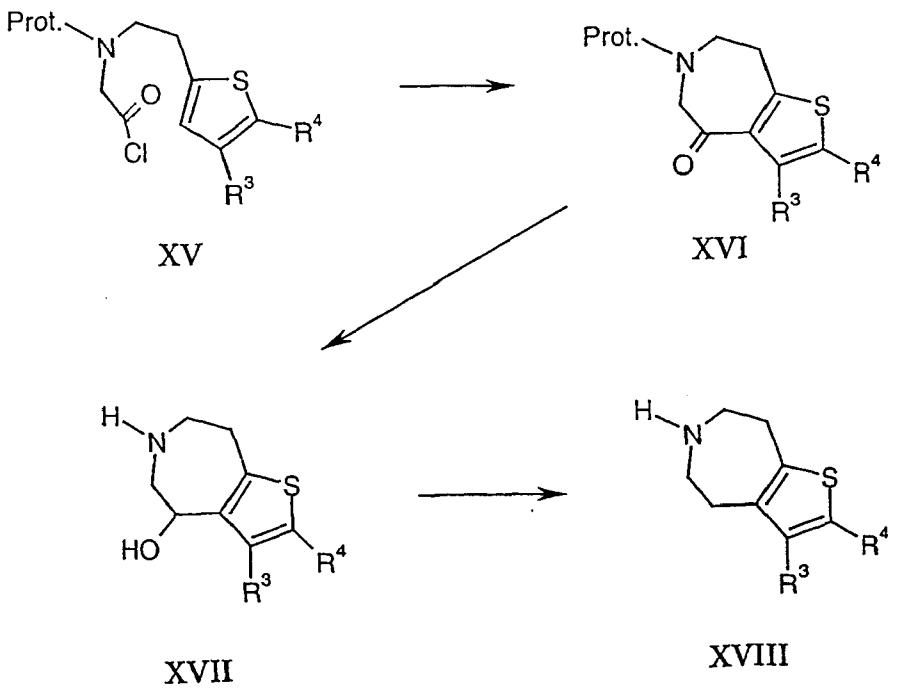
Optionally substituted 1,2,4,5-tetrahydro-benzo[d]azepine compounds III



III

are prepared as described in the Eur. Pat. Appl. EP 1 074 549 A2 (2001). The 5,6,7,8-tetrahydro-4H-thieno[2,3-d]azepine with R^3 and R^4 = H is known (*J. Heterocyclic Chem.* 1985, 22, 1011). Analogous 5,6,7,8-tetrahydro-4H-thieno[2,3-d]azepine compounds bearing substituents in the thiophene ring can be prepared in close analogy as outlined in scheme 5. Precursor acid chlorides XV bearing preferentially a tosyloxy protective function at the secondary nitrogen atom are cyclized in an inert solvent like 1,2-dichloroethane, dichloromethane or nitrobenzene in the presence of a Lewis acid catalyst like aluminium trichloride, tin tetrachloride or phosphorous pentachloride at temperatures between -40 °C and 80 °C to yield the protected ketones XVI. Hydroxy thieno[2,3-d]azepines XVII can be obtained by simultaneous reduction of the ketone function and removal of the N-tosyl protective function by treatment with sodium bis(methoxyethoxy)aluminium-hydride in toluene at reflux. The hydroxy thieno[2,3-d]azepines XVII can be further reduced to 5,6,7,8-tetrahydro-4H-thieno[2,3-d]azepines XVIII with stannous chloride in acetic acid in the presence of hydrochloric acid at temperatures between room temperature and 100 °C.

Scheme 5



XV XVI

XVII XVIII

The methods for the preparation of compounds of general formula I are described in more detail in examples 1 to 15.

The pharmaceutically acceptable salts can be manufactured readily according to methods known per se and taking into consideration the nature of the compound to be converted into a salt. Inorganic or organic acids such as, for example, hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid, phosphoric acid or citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like are suitable for the formation of pharmaceutically acceptable salts of basic compounds of formula I. Compounds which contain the alkali metals or alkaline earth metals, for example sodium, potassium, calcium, magnesium or the like, basic amines or basic amino acids are suitable for the formation or pharmaceutically acceptable salts of acidic compounds of formula I.

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

The compounds of the present invention are group I mGluR antagonists. Their pharmacological activity was tested using the following method:

Binding assay for the characterization of mGluR 1 antagonistic properties

Binding assay with tritiated 1-ethyl-2-methyl-6-oxo-4-(1,1,2-tritritio-1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-1,6-dihydro-pyrimidine-5-carbonitrile (Eur. Pat. Appl. EP 1 074 549 A2): HEK 293 cells were transiently transfected with the rat mGluR1a receptor. The cells were collected and washed 3 times with PBS. The cell pellets were frozen

at –80 °C. Membranes were prepared from HEK 293 cells transfected with the rat mGluR1a receptor and used in the binding experiments at 10 µg proteins per assay after resuspension in a HEPES NaOH 20mM, pH=7.4 binding buffer. 1-Ethyl-2-methyl-6-oxo-4-(1,1,2-tritritio-1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-1,6-dihydro-pyrimidine-5-carbonitrile (S.A 33.4 Ci/mmol) was used at 3 nM final concentration. The incubation with variable concentrations of potential inhibitors was performed for 1 hour at room temperature, the incubate was then filtered onto GF/B glass fiber filter preincubated 1 hour in PEI 0,1% and washed 3 times with 1ml of cold binding buffer. The radioactivity retained on the unifilter 96 was counted using a Topcount β counter. After correction for non specific binding the data were normalized and the IC_{50} value calculated using a 4 parameters logistic equation which was fitted to the inhibition curve.

The preferred compounds have an IC_{50} range of 0.001 – 10.0 µmol/l (B-IC_{50}).

In the table below are shown some specific activity data of preferred compounds:

	Example No.	B-IC_{50} (μM)
3-(2-methoxy-ethoxy)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile	1	3.0
3-amino-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile	2	0.027
3-dimethylamino-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile	3	1.38
3-(cyclopropylmethyl-amino)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile	4	0.005
3-(2-hydroxy-ethylamino)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile	5	0.031
(RS)-3-(2-hydroxy-propylamino)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile	6	0.027
3-hydrazino-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile	7	0.37
{2-[6-cyano-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazin-3-ylamino]-ethyl}-carbamic acid tert-butyl ester	8	0.027
3-(2-pyridin-3-yl-ethylamino)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile	9	0.029
6-ethyl-5-methyl-3-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-pyrazine-2-carbonitrile	12	0.006
5-ethyl-6-methyl-3-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-pyrazine-2-carbonitrile	12	0.103
3-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-pyrazine-2-carbonitrile	13	0.47
5-methyl-6-phenyl-3-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-pyrazine-2-carbonitrile	14	0.045
5-(2-hydroxy-ethylamino)-3-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-pyrazine-2-carbonitrile	15	0.5

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

administration can also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

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

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

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

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

Finally, as mentioned earlier, the use of compounds of formula I and of pharmaceutically acceptable salts thereof for the production of medicaments, especially for

the control or prevention of acute and/or chronic neurological disorders of the aforementioned kind, is also an object of the invention.

The following examples are provided for illustration of the invention. They should not be considered as limiting the scope of the invention, but merely as being representative thereof.

Example 1

3-(2-Methoxy-ethoxy)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile

a) 5-Chloro-3-methylsulfanyl-[1,2,4]triazine-6-carbonitrile

A solution of 500 mg (2.7 mmol) of 3-methylsulfanyl-5-oxo-4,5-dihydro-[1,2,4]triazine-6-carboxylic acid amide (J.J.Huang, *J.Org.Chem.* 1985, 50, 2293-2298; H.Wang et al., *Hua Hsueh Hsueh Pao* 1964, 30(2), 183-192; CA Vol. 61, 8311b) in 38 ml (408 mmol) of phosphorus oxychloride was heated to reflux during 1.5 h. After cooling of the dark brown reaction mixture, the excess of phosphorus oxychloride was evaporated under reduced pressure. To distroy residues of phosphorus oxychloride and to neutralize the reaction mixture, the resulting red-brown oily residue was dissolved in 15 ml of toluene and the solution added to an ice-cold saturated aqueous solution of sodium hydrogencarbonate. The organic phase was diluted with 100 ml of dichloromethane, separated from the aqueous phase, dried over sodium sulfate, and evaporated under reduced pressure. The resulting 5-chloro-3-methylsulfanyl-[1,2,4]triazine-6-carbonitrile was obtained as a brown oil and was used in the following reactions without further purification.

b) 3-Methylsulfanyl-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile

A solution of 395 mg (2.7 mmol) of 2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride [*J. Heterocycl. Chem.* 1971, 8(5), 779-83] in 5 ml of ethanol was treated at room temperature with 0.92 ml (5.4 mmol) of Huenig's base and, thereupon, with a solution of 501 mg (2.7 mmol) of crude 5-chloro-3-methylsulfanyl-[1,2,4]triazine-6-carbonitrile in 5 ml of ethanol. The dark brown reaction mixture was stirred during 18 h at room temperature. For the working-up, the product, partially precipitated in pure form, was filtered and the resulting mother liquor evaporated under reduced pressure. The residue was chromatographed on silica gel with a 2:1 v/v mixture of hexane and ethylacetate as the eluent. In total, 470 mg (58.5% of theory) of 3-methylsulfanyl-5-(1,2,4,5-tetrahydro-

benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile were obtained in the form of a beige powder; MS: 298 $(M+H)^+$.

c) 3-(2-Methoxy-ethoxy)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile

Under an argon atmosphere at 0° C, a solution of 25.6 mg (0.34 mmol) of 2-methoxy-ethanol in 2 ml of tetrahydrofurane was treated with 15 mg (0.34 mmol) of sodium hydride (55% dispersion in refined oil) and stirred during 15 min. To this mixture, a solution of 100 mg (0.34 mmol) of 3-methylsulfanyl-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile in 3 ml of tetrahydrofurane was added and stirring continued for 18 h at 40 °C. The yellow solution was evaporated under reduced pressure and the residue (141 mg) was chromatographed on silica gel with a 99:1 v/v mixture of dichloromethane and methanol as eluent. Thus were obtained 10 mg (9% of theory) of 3-(2-methoxy-ethoxy)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile as a light yellow solid; MS: 326 $(M+H)^+$.

Example 2

3-Amino-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile

A dispersion of 200 mg (0.67 mmol) of 3-methylsulfanyl-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile, which was obtained according to the method as described in example 1b, and 1.0 ml of ammonium hydroxide (1.34 M) was heated under stirring in a sealed tube at 140 °C overnight. To complete the reaction, another 1.0 ml of ammonium hydroxide (1.34 M) was added. Heating was continued under the aforementioned conditions for 18 h. The limpid solution was evaporated under reduced pressure and the residue was chromatographed on silica gel with a 95:5 v/v mixture of dichloromethane and methanol as the eluent. There were obtained 40 mg (22% of theory) of 3-amino-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile as a light yellow solid; MS: 267 $(M+H)^+$.

Example 3

3-Dimethylamino-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile

In an analogous manner as described in example 2, reaction of 3-methylsulfanyl-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile with dimethylamine (33% solution in absolute ethanol) in a sealed tube at 110 °C yielded 3-dimethylamino-5-

(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile as a light brown amorphous solid; MS: 295 $(M+H)^+$.

Example 4

3-(Cyclopropylmethyl-amino)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile

A mixture of 150 mg (0.50 mmol) of 3-methylsulfanyl-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile as prepared in example 1b and 74 mg (1.0 mmol) of aminomethyl-cyclopropane in 5 ml of dioxane was stirred at 120 °C overnight. The solution was evaporated under reduced pressure and the residue was chromatographed on silica gel with a 98:2 v/v mixture of dichloromethane and methanol as the eluent. There were obtained 57 mg (35% of theory) of 3-(cyclopropylmethyl-amino)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile as a white solid; MS: 321 $(M+H)^+$.

Example 5

3-(2-Hydroxy-ethylamino)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile

In analogy to the procedure as described in example 4 the 3-methylsulfanyl-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile was reacted with ethanolamine in dioxane at 140 °C overnight to give 3-(2-hydroxy-ethylamino)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile as a light yellow solid; MS: 311 $(M+H)^+$.

Example 6

(RS)-3-(2-Hydroxy-propylamino)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile

In analogy to the procedure as described in example 4 the 3-methylsulfanyl-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile was reacted with (RS)-1-amino-2-propanol in dioxane at 120 °C overnight to give (RS)-3-(2-hydroxy-propylamino)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile as a white solid; MS: 325 $(M+H)^+$.

Example 7

3-Hydrazino-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile

In analogy to the procedure as described in example 4 the 3-methylsulfanyl-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile was reacted with hydrazine hydrate in dioxane at 140 °C during 3 hours to give 3-hydrazino-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile as a yellow amorphous powder; MS: 282 $(M+H)^+$.

Example 8

{2-[6-Cyano-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazin-3-ylamino]-ethyl}-carbamic acid tert-butyl ester

In analogy to the procedure described in example 4 the 3-methylsulfanyl-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile was reacted with (2-aminoethyl)-carbamic acid tert-butyl ester in dioxane at 120 °C overnight to give {2-[6-cyano-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazin-3-ylamino]-ethyl}-carbamic acid tert-butyl ester as a white solid; MS: 410 $(M+H)^+$.

Example 9

3-(2-Pyridin-3-yl-ethylamino)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile

A solution of 120 mg (0.40 mmol) of 3-methylsulfanyl-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile in 5 ml of dichloromethane was treated at room temperature with 109 mg (0.44 mmol) of 3-chloro-perbenzoic acid (70%). After 2 hours the reaction mixture was evaporated under reduced pressure, and, without working-up and characterization, the resulting crude 3-methanesulfonyl-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile was directly treated with a solution of 108 mg (0.88 mmol) of 3-(2-aminoethyl)pyridine in 10 ml of dioxane. The reaction mixture was then stirred at 80 °C overnight. The reaction mixture was then evaporated under reduced pressure and the residue obtained directly chromatographed on silica gel with a 95:5:0.1 v/v/v mixture of dichloromethane, methanol and ammonium hydroxide as the eluent. There were obtained 55 mg (37% of theory) of 3-(2-pyridin-3-yl-ethylamino)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile as a white amorphous solid; MS: 372 $(M+H)^+$.

Example 10

3-Hydroxy-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile

A solution of 200 mg (0.67 mmol) of 3-methylsulfanyl-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile in 10 ml of dichloromethane was cooled to 0 °C and treated with 332 mg (1.35 mmol) of 3-chloro-perbenzoic acid (70%). The reaction mixture was warmed up to room temperature and stirred overnight. For the working-up, the reaction mixture was diluted with 10 ml of dichloromethane and extracted twice with 10 ml of a saturated solution of sodium hydrogencarbonate. The combined organic phases were dried over sodium sulfate, and evaporated under reduced pressure. The resulting residue, 170 mg of a yellow powder, was purified by chromatograhy on silica gel with a 98:2 mixture of dichloromethane and methanol as eluent. There were obtained 154 mg (86% of theory) of 3-hydroxy-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile as a yellowish solid; MS: 266 (M-H).

Example 11

3-(2-Amino-ethylamino)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile trifluoro-acetate

To a solution of 60 mg (0.15 mmol) of {2-[6-cyano-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazin-3-ylamino]-ethyl}-carbamic acid tert-butyl ester as prepared in example 8 in 2 ml of dichloromethane were added 0.2 ml of trifluoroacetic acid. The reaction mixture was stirred at room temperature for one hour and then evaporated under reduced pressure. The solid residue was dispersed in ether. The resulting solid was filtered and gave 30 mg (47% of theory) of 3-(2-amino-ethylamino)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile trifluoro-acetate as an off-white solid; MS: 310 $(M+H)^+$.

Example 12

12-1) 5-Ethyl-6-methyl-3-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-pyrazine-2-carbonitrile

and

12-2) 6-Ethyl-5-methyl-3-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-pyrazine-2-carbonitrile

a) 5-Ethyl-6-methyl-3-oxo-3,4-dihydro-pyrazine-2-carboxylic acid amide and 6-ethyl-5-methyl-3-oxo-3,4-dihydro-pyrazine-2-carboxylic acid amide

A solution of 8.32 g (80.61 mmol) 2-amino-malonic acid diamide and 9.75 g (83.26 mmol) of 2,3-pentanedione in 60 ml of water was heated under reflux for 18 hours. After cooling to room temperature the crystals formed were collected by filtration and dried in vacuo. There were thus obtained 9.52 g (52.54 mmol, 65.2% of theory) of a 3:2 or a 2:3 mixture of the 6-ethyl-5-methyl-3-oxo-3,4-dihydro-pyrazine-2-carboxylic acid amide and the 5-ethyl-6-methyl-3-oxo-3,4-dihydro-pyrazine-2-carboxylic acid amide as yellow solid; MS: 181 $(M)^+$.

b) 3-Chloro-6-ethyl-5-methyl-pyrazine-2-carbonitrile and 3-chloro-5-ethyl-6-methyl-pyrazine-2-carbonitrile (1:1 mixture of the two isomers)

1.81 g (10.0 mmol) of the 3:2 or 2:3 mixture of the 6-ethyl-5-methyl-3-oxo-3,4-dihydro-pyrazine-2-carboxylic acid amide and the 5-ethyl-6-methyl-3-oxo-3,4-dihydro-pyrazine-2-carboxylic acid amide were suspended in 4.2 ml (30 mmol) of triethylamine. Then, 30 ml of phosphorus oxychloride were slowly added between 0°C and 5°C and the reaction mixture heated under reflux for 3 hours. It was then cooled to 20°C, 5.3 g (25 mmol) of phosphorus pentachloride were added and the reaction mixture heated again under reflux for 3 hours. It was then added to water while maintaining a temperature of 20°C to 25°C. The aqueous phase was subsequently extracted 5 times with 100 ml of ether and the combined ether phases washed with saturated sodium hydrogen carbonate solution, dried over magnesium sulfate and evaporated under reduced pressure. The residue formed was chromatographed on silica gel using a 1:1 v/v mixture of dichloromethane and hexane as eluent giving 1.0 g (5.5 mmol, 55% of theory) of a 1:1 mixture of the 3-chloro-6-ethyl-5-methyl-pyrazine-2-carbonitrile and the 3-chloro-5-ethyl-6-methyl-pyrazine-2-carbonitrile in form of an orange red oil; MS: 181 $(M)^+$.

c) 5-Ethyl-6-methyl-3-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-pyrazine-2-carbonitrile and 6-ethyl-5-methyl-3-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-pyrazine-2-carbonitrile

A solution of 0.300 g (1.65 mmol) of the 1:1 mixture of the 3-chloro-6-ethyl-5-methyl-pyrazine-2-carbonitrile and the 3-chloro-5-ethyl-6-methyl-pyrazine-2-carbonitrile, of 0.395 g (1.30 mmol) of 2,3,4,5-tetrahydro-1H-benzo[d]azepine hydrochloride (*J. Heterocycl. Chem.* 1971, 8(5), 779-83) and of 0.566 g (2.60 mmol) of N-ethyl-diisopropylamine in 1.0 ml of N,N-dimethylformamide was stirred at room temperature for 60 hours and then at 60°C for 18 hours. The reaction mixture was subsequently poured into 50 ml of an ice/water mixture and extracted 3 times with 50 ml of ethylacetate. The combined ethylacetate phases were dried over magnesium sulfate and evaporated under reduced pressure. The residue formed was then chromatographed on silica gel using dichloromethane as eluent giving 0.086 g (0.29 mmol, 18% of theory) of the 6-ethyl-5-methyl-3-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-pyrazine-2-carbonitrile as yellowish solid after crystallization from dichlormethane/pentane; MS: 293 $(M+H)^+$; and 0.074 g (0.25 mmol, 15% of theory) of the 5-ethyl-6-methyl-3-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-pyrazine-2-carbonitrile as yellowish solid; MS: 293 $(M+H)^+$.

Example 13

3-(1,2,4,5-Tetrahydro-benzo[d]azepin-3-yl)-pyrazine-2-carbonitrile

In analogy to the procedure as described in example 12 the 2-chloro-3-cyanopyrazine (*J. Chem. Soc., Perkin Trans. I* 1991, 11, 2877-81) was treated with 2,3,4,5-tetrahydro-1H-benzo[d]azepine hydrochloride (*J. Heterocycl. Chem.* 1971, 8(5), 779-83) and N-ethyl-diisopropylamine in N,N-dimethylformamide at room temperature followed by 60°C to yield the 3-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-pyrazine-2-carbonitrile as light yellow solid; MS: 251 $(M+H)^+$.

Example 14

5-Methyl-6-phenyl-3-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-pyrazine-2-carbonitrile

In analogy to the procedure described in example 12 1-phenyl-1,2-propanedione and 2-aminomalonamide were heated in an aqueous solution to give 5-methyl-3-oxo-6-phenyl-3,4-dihydro-pyrazine-2-carboxylic acid amide. Then, the 5-methyl-3-oxo-6-phenyl-3,4-dihydro-pyrazine-2-carboxylic acid amide was treated with triethylamine and phosphorus pentachloride in phosphorus oxychloride at reflux to give the 3-chloro-5-methyl-6-phenyl-pyrazine-2-carbonitrile. The 3-chloro-5-methyl-6-phenyl-pyrazine-2-carbonitrile was finally treated with 2,3,4,5-tetrahydro-1H-benzo[d]azepine hydrochloride (*J. Heterocycl.*

Chem. 1971, 8(5), 779-83) and N-ethyldiisopropylamine in N,N-dimethylformamide at room temperature to yield the 5-methyl-6-phenyl-3-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-pyrazine-2-carbonitrile as yellow amorphous solid; MS: 341 $(M+H)^+$.

Example 15

5-(2-Hydroxy-ethylamino)-3-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-pyrazine-2-carbonitrile

a) 3-Bromo-5-chloro-pyrazine-2-carbonitrile

A solution of 0.309 g (2.00 mmol) of the 3-amino-5-chloro-pyrazine-2-carbonitrile (*J. Org. Chem.* 1975, 40, 2341-2347) in 5.0 ml of acetonitrile was slowly added at a temperature of 65 °C to a suspension of 0.903 g (4.0 mmol) of copper(II)bromide and 0.344 g (3.0 mmol) of tert.-butyl nitrite in 20.0 ml of acetonitrile. The reaction mixture was stirred at 65 °C for 1 hour, then cooled to room temperature. It was subsequently poured into 50 ml of an ice/water mixture and extracted 3 times with 50 ml of dichloromethane. The combined dichloromethane phases were dried over magnesium sulfate and evaporated under reduced pressure. The residue formed was chromatographed on silica gel with a 4:1 to 0:10 v/v gradient of hexane and dichloromethane as the eluent giving 0.333 g (1.53 mmol, 76.2 % of theory) of the 3-bromo-5-chloro-pyrazine-2-carbonitrile as light yellow amorphous solid; MS: 218 $(M)^+$.

b) 3-Bromo-5-(2-hydroxy-ethylamino)-pyrazine-2-carbonitrile

0.061 g (1.00 mmol) of ethanolamine were added slowly at room temperature to a solution of 0.218 g (1.0 mmol) of the 3-bromo-5-chloro-pyrazine-2-carbonitrile and 0.264 g (2.0 mmol) of N-ethyldiisopropylamine in 15.0 ml of dioxane. The reaction mixture was stirred at room temperature for 18 hours. It was subsequently poured into 50 ml of an ice/ water/ sodium hydrogen carbonate mixture and extracted 3 times with 50 ml of ethylacetate. The combined ethylacetate phases were dried over magnesium sulfate and evaporated under reduced pressure. The residue formed was chromatographed on silica gel with a 100:0 to 95:5 v/v gradient of dichloromethane and methanol as the eluent giving 0.131 g (0.539 mmol, 53.9 % of theory) of the 3-bromo-5-(2-hydroxy-ethylamino)-pyrazine-2-carbonitrile as yellow amorphous solid; MS: 243 $(M)^+$.

c) 5-(2-Hydroxy-ethylamino)-3-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-pyrazine-2-carbonitrile

0.415 g (3.00 mmol) of potassium carbonate were added slowly at room temperature to a solution of 0.243 g (1.0 mmol) of the 3-bromo-5-(2-hydroxy-ethylamino)-pyrazine-2-carbonitrile and 0.220 g (1.2 mmol) of the 2,3,4,5-tetrahydro-1H-benzo[d]azepine hydrochloride (*J. Heterocycl. Chem.* 1971, 8(5), 779-83) in 10.0 ml of N,N-dimethyl-formamide. The reaction mixture was stirred at room temperature for 64 hours and at 80 °C for 5 hours. It was subsequently poured into 50 ml of an ice/water mixture and extracted 3 times with 50 ml of dichloromethane. The combined dichloromethane phases were dried over magnesium sulfate and evaporated under reduced pressure. The residue formed was chromatographed on silica gel with a 9:1 to 0:10 v/v gradient of hexane and ethylacetate as the eluent giving 0.308 g (1.0 mmol, 100% of theory) of the 5-(2-hydroxy-ethylamino)-3-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-pyrazine-2-carbonitrile as light yellow amorphous solid; MS: 310 $(M+H)^+$.

Example A

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

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

Example B

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

	mg/Tablet
Active ingredient	200
Powdered lactose	100
White corn starch	64
Polyvinylpyrrolidone	12
Na carboxymethylstarch	20
Magnesium stearate	4
Tablet weight	400

Example C

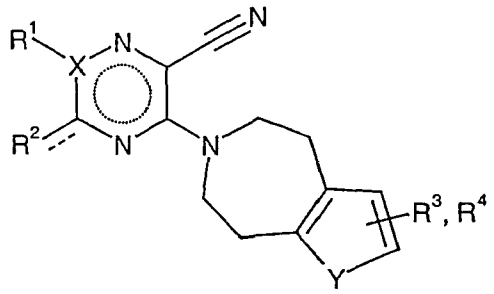
Capsules of the following composition are produced:

	mg/Capsule
Active ingredient	50
Crystalline lactose	60
Microcrystalline cellulose	34
Talc	5
Magnesium stearate	1
Capsule fill weight	150

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

Claims

1. Compounds of the general formula



I

wherein

R^1 signifies hydrogen, lower alkyl, lower alkenyl, or unsubstituted phenyl or phenyl substituted in meta or para positions with one or more substituents selected from the group consisting of lower alkyl, lower alkoxy or halogen; or is absent, if X is –N= or =N-;

R^2 signifies hydrogen, lower alkyl, lower alkenyl, =O, -S-lower alkyl, $-SO_2$-lower alkyl or
-OR, $-O(CHR)_{m+1}-OR$, $-NR_2$, $-NH-NR_2$, $-N(R)(CHR)_{m+1}-OR$,
$-N(R)(CHR)_m$-pyridino, $-N(R)(CHR)_n-(C_3-C_6)$cycloalkyl,
$-N(R)(CHR)_m(CR_2)-NR_2$, or $-N(R)(CHR)_{m+1}-NH-C(O)-O$-lower alkyl;

m is 1, 2, 3, 4, 5 or 6;

n is 0, 1, 2, 3, 4 or 5;

R signifies hydrogen, lower alkyl or lower alkenyl, independently from each other, if more than one R is present;

X signifies –N=, =N-, >C= or =C<; and

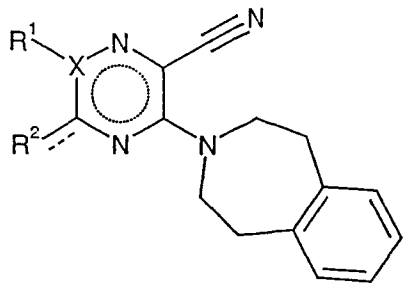
the dotted line may be a bond,

Y signifies –CH=CH-, $-CH=CR^3-$, $-CR^3=CH-$, $-CR^3=CR^4-$ or S; and

R^3, R^4 signify independently from each other hydrogen, lower alkyl, lower alkoxy or halogen with the proviso, that if Y represents a vinylene group, only one group R^3 and one group R^4 may be present in the entire benzene ring;

as well as their pharmaceutically acceptable salts.

2. Compounds in accordance with claim 1 having the general formula



I-A

wherein

R^1 signifies hydrogen, lower alkyl, lower alkenyl, or unsubstituted phenyl or phenyl substituted in meta or para positions with one or more substituents selected from the group consisting of lower alkyl, lower alkoxy or halogen, or is absent, if X is –N= or =N-;

R^2 signifies hydrogen, lower alkyl, lower alkenyl, =O, -S-lower alkyl, $-SO_2$-lower alkyl or
-OR, $-O(CHR)_{m+1}-OR$, $-NR_2$, $-NH-NR_2$, $-N(R)(CHR)_{m+1}-OR$, $-N(R)(CHR)_m$-pyridino, $-N(R)(CHR)_n-(C_3-C_6)$cycloalkyl, $-N(R)(CHR)_m(CR_2)-NR_2$, or $-N(R)(CHR)_{m+1}-NH-C(O)-O$-lower alkyl;

m is 1, 2, 3, 4, 5 or 6;

n is 0, 1, 2, 3, 4 or 5;

R signifies hydrogen, lower alkyl or lower alkenyl, independently from each other, if more than one R is present;

X signifies –N=, =N-, >C= or =C<; and

the dotted line may be a bond,

as well as their pharmaceutically acceptable salts.

3. Compounds of formula I-A in accordance with claim 2, wherein R^1 is absent and X is –N= or =N-.

4. Compounds of formula I-A in accordance with claims 2 and 3, wherein R^2 signifies $-NR_2$, $-NH-NR_2$, $-N(R)(CHR)_{m+1}-OR$, $-N(R)(CHR)_m$-pyridino, $-N(R)(CHR)_n-(C_3-C_6)$cycloalkyl, $-N(R)(CHR)_m(CR_2)-NR_2$, or $-N(R)(CHR)_{m+1}-NH-C(O)-O$-lower alkyl.

5. Compounds of formula I-A in accordance with claim 4, wich compounds are selected from a group consisting of

3-Amino-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile,

3-hydrazino-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile, or

{2-[6-cyano-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazin-3-ylamino]-ethyl}-carbamic acid tert-butyl ester.

6. Compounds of formula I-A in accordance with claims 2 and 3, wherein R^2 signifies $-N(R)(CHR)_{m+1}-OR$, $-N(R)(CHR)_m$-pyridino, or $-N(R)(CHR)_n-(C_3-C_6)$cycloalkyl.

7. Compounds of formula I-A in accordance with claim 6, which are selected from a group consisting of

3-(cyclopropylmethyl-amino)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile,

3-(2-hydroxy-ethylamino)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile,

(RS)-3-(2-hydroxy-propylamino)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile, or

3-(2-pyridin-3-yl-ethylamino)-5-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-[1,2,4]triazine-6-carbonitrile.

8. Compounds of formula I-A in accordance with claim 2, wherein X signifies >C= or =C<.

9. Compounds of formula I-A in accordance with claims 2 and 8, wherein R^1 and R^2 are lower alkyl.

10. Compounds of formula I-A in accordance with claim 9, which compounds are selected from a group consisting of

5-ethyl-6-methyl-3-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-pyrazine-2-carbonitrile, or

6-ethyl-5-methyl-3-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-pyrazine-2-carbonitrile.

11. Compounds of formula I-A in accordance with claims 2 and 8, wherein R^1 signifies ethyl.

12. Compounds of formula I-A in accordance with claims 2 and 8, wherein R^1 signifies unsubstituted phenyl or phenyl substituted in meta or para positions with one or more substituents selected from the group consisting of lower alkyl, lower alkoxy or halogen.

13. A compound of formula I-A in accordance with claim 12, which compound is 5-methyl-6-phenyl-3-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-pyrazine-2-carbonitrile.

14. Compounds of formula I-A in accordance with claims 2 and 8, wherein R^2 signifies $-N(R)(CHR)_{m+1}-OR$ with R signifying independently from each other hydrogen, lower alkyl or lower alkenyl.

15. A compound of formula I-A in accordance with claim 15, which compound is 5-(2-hydroxy-ethylamino)-3-(1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-pyrazine-2-carbonitrile.

16. Compounds of formula I in accordance with claims 1 to 15 as well as their pharmaceutically acceptable salts for use in the control or prevention of acute and/or chronic neurological disorders.

17. A medicament comprising a compound of formula I according to any one of claims 1 to 15 as well as pharmaceutically acceptable salts thereof and pharmaceutically acceptable excipients.

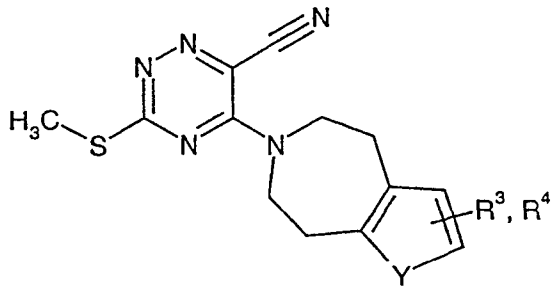
18. A medicament in accordance with claim 17 for the control or prevention of diseases which are mediated by metabotropic glutamate receptor antagonists, such as acute and/or chronic neurological disorders.

19. The use of compounds of formula I in accordance with any one of claims 1 to15 as well as their pharmaceutically acceptable salts for the manufacture of medicaments for the control or prevention of diseases which are mediated by metabotropic glutamate receptor antagonists.

20. The use of compounds of formula I in accordance with claims 1 to 15 as well as their pharmaceutically acceptable salts for the manufacture of medicaments for the control or prevention of acute and/or chronic neurological disorders.

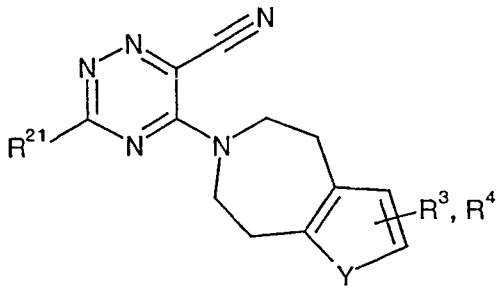
21. A process for the manufacture of compounds of formula I according to any one of claims 1 to 15 as well as of pharmaceutically acceptable salts thereof, which process comprises

a) reacting the compound of the formula



I-2

with nucleophiles to obtain a compound of formula



I-1

wherein R^{21} signifies -OR, $-O(CHR)_{m+1}-OR$, $-NR_2$, $-NH-NR_2$, $-N(R)(CHR)_{m+1}-OR$, $-N(R)(CHR)_m$-pyridino, $-N(R)(CHR)_n-(C_3-C_6)$cycloalkyl, $-N(R)(CHR)_m(CR_2)-NR_2$, or $-N(R)(CHR)_{m+1}$-NH-C(O)-O-lower alkyl as defined before,

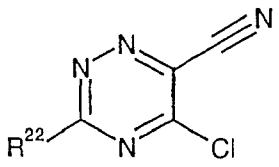
and, if desired,

converting a functional group of R^{21} in a compound of formula I-1 into another functional group to obtain another compound of formula I-1,

and, if desired,

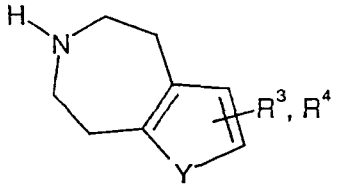
converting a compound of formula I-1 into a pharmaceutically acceptable salt; or

b) reacting a compound of the formula



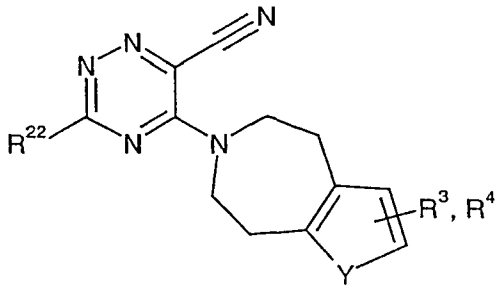
II-1

wherein R^{22} signifies alkyl, with the compound of formula



III

to obtain a compound of formula

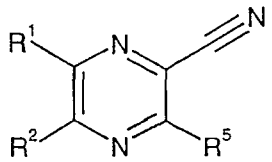


I-3

and, if desired,

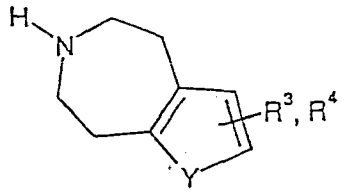
converting a compound of formula I-3 into a pharmaceutically acceptable salt; or

c) reacting a compound of the formula



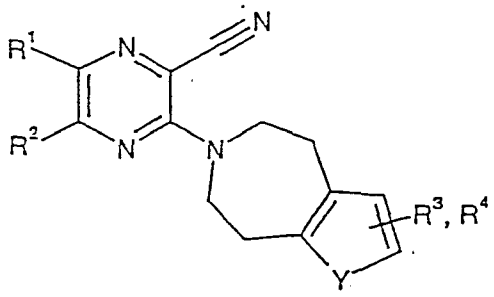
II-2

wherein R^5 signifies halogen, with the compound of formula



III

to obtain a compound of formula



I-4

and, if desired,

converting a functional group of R^2 in a compound of formula I-4 into another functional group to obtain another compound of formula I-4,

and, if desired,

converting a compound of formula I-4 into a pharmaceutically acceptable salt.

22. Compounds of formula I in accordance with claims 1 to 15, when manufactured according to a process in accordance with claim 21.

23. A substance or composition for use in a method for the control or prevention of diseases which are mediated by metabotropic glutamate receptor antagonists, said substance or composition comprising a compound of formula I in accordance with any one of claims 1 to 15 as well as its pharmaceutically acceptable salt, and said method comprising administering said substance or composition.

24. A substance or composition for use in a method for the control or prevention of acute and/or chronic neurological disorders, said substance or composition comprising a compound of formula I in accordance with claims 1 to 15 as well as its pharmaceutically acceptable salt, and said method comprising administering said substance or composition.

25. The invention as hereinbefore described.

26. A compound according to any one of claims 1 to 16 or 22, substantially as herein described and illustrated.

27. A medicament according to claim 17 or claim 18, substantially as herein described and illustrated.

28. Use according to claim 19 or claim 20, substantially as herein described and illustrated.

29. A process according to claim 21, substantially as herein described and illustrated.

30. A substance or composition for use in a method of treatment or prevention according to claim 23 or claim 24, substantially as herein described and illustrated.

31. A new compound, a new medicament, a new use of a compound as claimed in any one of claims 1 to 15, a new process for the manufacture of a compound, or a substance or composition for a new use in a method of treatment or prevention, substantially as herein described.