The aminochromane, aminothiochromane and amino-1,2,3,4-tetrahydroquinoline derivatives are GlyT1 inhibitors.

Abstract:
The present invention relates to aminochromane, aminothiochromane and amino-1,2,3,4-tetrahydroquinoline derivatives of the formula (I) or a physiologically tolerated salt thereof. The invention relates to pharmaceutical compositions comprising such aminochromane, aminothiochromane and amino-1,2,3,4-tetrahydroquinoline derivatives, and the use of such aminochromane, aminothiochromane and amino-1,2,3,4-tetrahydroquinoline derivatives for therapeutic purposes. The aminochromane, aminothiochromane and amino-1,2,3,4-tetrahydroquinoline derivatives are GlyT1 inhibitors.
Aminochromane, aminothiochromane and amino-1,2,3,4-tetrahydroquinoline derivatives, pharmaceutical compositions containing them, and their use in therapy

Background of the Invention

The present invention relates to aminochromane, aminothiochromane and amino-1,2,3,4-tetrahydroquinoline derivatives, pharmaceutical compositions comprising such aminochromane, aminothiochromane and amino-1,2,3,4-tetrahydroquinoline derivatives, and the use of such aminochromane, aminothiochromane and amino-1,2,3,4-tetrahydroquinoline derivatives for therapeutic purposes. The aminochromane, aminothiochromane and amino-1,2,3,4-tetrahydroquinoline derivatives are GlyT1 inhibitors.

Dysfunction of glutamatergic pathways has been implicated in a number of disease states in the human central nervous system (CNS) including but not limited to schizophrenia, cognitive deficits, dementia, Parkinson disease, Alzheimer disease and bipolar disorder. A large number of studies in animal models lend support to the NMDA hypofunction hypothesis of schizophrenia.

NMDA receptor function can be modulated by altering the availability of the co-agonist glycine. This approach has the critical advantage of maintaining activity-dependent activation of the NMDA receptor because an increase in the synaptic concentration of glycine will not produce an activation of NMDA receptors in the absence of glutamate. Since synaptic glutamate levels are tightly maintained by high affinity transport mechanisms, an increased activation of the glycine site will only enhance the NMDA component of activated synapses.

Two specific glycine transporters, GlyT1 and GlyT2 have been identified and shown to belong to the Na/Cl-dependent family of neurotransmitter transporters which includes taurine, gamma-aminobutyric acid (GABA), proline, monoamines and orphan transporters. GlyT1 and GlyT2 have been isolated from different species and shown to have only 50% identity at the amino acid level. They also have a different pattern of expression in mammalian central nervous system, with GlyT2 being expressed in spinal cord, brainstem and cerebellum and GlyT1 present in these regions as well as forebrain areas such as cortex, hippocampus, septum and thalamus. At the cellular level, GlyT2 has been reported to be expressed by glycinergetic nerve endings in rat spinal cord whereas GlyT1 appears to be preferentially expressed by glial cells. These expression studies have led to the suggestion that GlyT2 is predominantly responsible for glycine uptake at glycinerergic synapses whereas GlyT1 is involved in monitoring glycine concentration in the vicinity of NMDA receptor
expressing synapses. Recent functional studies in rat have shown that blockade of GlyT1 with the potent inhibitor (N-[3-(4'-fluorophenyl)-3-(4'-phenylphenoxy)propyl])-sarcosine (NFPS) potentiates NMDA receptor activity and NMDA receptor-dependent long-term potentiation in rat.

Molecular cloning has further revealed the existence of three variants of GlyT1, termed GlyT1a, GlyT1b and GlyT1c, each of which displays a unique distribution in the brain and peripheral tissues. The variants arise by differential splicing and exon usage, and differ in their N-terminal regions.

The physiological effects of GlyT1 in forebrain regions together with clinical reports showing the beneficial effects of GlyT1 inhibitor sarcosine in improving symptoms in schizophrenia patients suggest that selective GlyT1 inhibitors represent a new class of antipsychotic drugs.

Glycine transporter inhibitors are already known in the art, for example:
Further glycine transporter inhibitors are known from the following documents.

WO 2009024611 describes 4-benzylaminoquinolines of formula:

\[
\text{(I)}
\]

WO 2009121872 describes tetrahydroisoquinoline of formula:

\[
\text{(I)}
\]

WO 2010092180 describes aminotetraline derivatives of formula:
WO 2010092181 describes heterocyclic compounds of formula:

\[
\begin{align*}
\text{A} & \quad \text{R}^2 \\
\text{X}^2 & \quad \text{X}^3 \\
\text{N} & \quad \text{R}^4 \\
\text{R}^5 &
\end{align*}
\]

WO 2012020131 describes aminoindane derivatives of formula:

\[
\begin{align*}
\text{A} & \quad \text{R}^2 \\
\text{X}^2 & \quad \text{X}^3 \\
\text{N} & \quad \text{R}^4 \\
\text{R}^5 &
\end{align*}
\]

WO 2012020130 describes phenalkylamine derivatives of formula:

\[
\begin{align*}
\text{R}^2 & \quad \text{R}^3 \\
\text{Y}^1 & \quad \text{Y}^2 \\
\text{N} & \quad \text{R}^4 \\
\text{R}^5 &
\end{align*}
\]

WO 2012020133 describes tetraline and indane derivatives of formula:
WO 2012152915 describes benzazepine derivatives of formula:

![Benzazepine Derivative](image1)

WO 2012020134 describes phenalkylamine derivatives of formulae:

![Phenalkylamine Derivative](image2)

WO 2013020930 describes aminochromane, aminothiochromane and amino-1,2,3,4-tetrahydroquinoline derivatives of formula:

![Aminochromane Derivative](image3)
WO 2013072520 describes N-substituted aminobenzocycloheptene, aminotetraline, aminoindane and phenalkylamine derivatives of formula:

![Structure](image1)

![Structure](image2)

![Structure](image3)

![Structure](image4)

WO 2013120835 describes isoindoline derivatives of formula:
It was one object of the present invention to provide further glycine transporter inhibitors. It was a further object of the present invention to provide glycine transporter inhibitors which combine high stability with high affinity. It was a further object of the present invention to provide glycine transporter inhibitors which show favorable efflux properties. It was a further object of the present invention to provide glycine transporter inhibitors which combine high stability and high affinity with favorable efflux properties.

**Summary of the Invention**

The present invention relates to aminochromane, aminothiochromane and amino-1,2,3,4-tetrahydroquinoline derivatives of the formula (I)

![Chemical Structure](image)

wherein

A is a 5- or 6-membered ring;

R¹ is hydrogen, alkyl, cycloalkylalkyl, halogenated alkyl, trialkylsilylalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alky carbonylaminoalkyl, alkyloxycarbonylaminoalkyl, alkaminocarbonylaminoalkyl, dialkylaminocarbonylaminoalkyl, alkylsulfonylaminoalkyl, (optionally substituted arylalkyl)aminoalkyl, optionally substituted arylalkyl, optionally substituted heterocyclylalkyl, cycloalkyl, alkylcarbonyl, alkoxy carbonyl, halogenated alkoxy carbonyl, aryloxycarbonyl, aminocarbonyl, alkyl-
minocarbonyl, (halogenated alkyl)aminocarbonyl, arylaminocarbonyl, alkenyl, alkynyl, optionally substituted aryl, hydroxy, alkoxy, halogenated alkoxy, hydroxyalkoxy, alkoxyalkoxy, aminoalkoxy, alkylationalkoxy, dialkylationalkoxy, alkylcarbonylaminalkoxy, arylcarbonylaminalkoxy, alkoxycarbonylaminalk oxy, arylalkoxy, alkylsulfon ylaminalkoxy, (halogenated alkyl)sulfon ylaminalkoxy, ary lsulfon ylaminalkoxy, (arylalkyl)sulfon ylaminalkoxy, heterocyclylsulfon ylaminalkoxy, heterocyclylalkoxy, arylazoxy, heterocyclylazoxy, alkylthio, halogenated alkylthio, alky lamino, (halogenated alkyl)amino, dialkylationamino, di-(halogenated alkyl)amino, alkylcarbonylamino, (halogenated alkyl)carbonylamino, arylcarbonylamino, alkylsulfon ylamino, (halogenated alkyl)sulfon ylamino, arylsulfon ylamino or optionally substituted heterocyclyl;

W is -NR 7- or a bond;

A 1 is optionally substituted alkylene or a bond;

Q is -S(0) 2- or -C(O)-;

Y is -NR 8- or a bond;

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

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

X 1 is >N- or >CH-;

R 6 is hydrogen, halogen, alkyl, halogenated alkyl, -CN, hydroxy, alkoxy or halogenated alkoxy, or two radicals R 6 together with the carbon atom to which they are attached form a carbonyl group;

R 2 is hydrogen, halogen, alkyl, halogenated alkyl, -CN, alkenyl, alkynyl, optionally substituted aryl, hydroxy, alkoxy, halogenated alkoxy, alkoxyalkoxy, arylal koxy, alkylcarbonyloxy, alkylthio, alkylsulfanyl, alkylsulfon yl, aminosulfon yl, amino, alky lamino, alkenylamino, nitro or optionally substituted heterocyclyl, or two radicals R 2 together with the ring atoms of A to which they are bound form a 5- or 6 membered ring;

A 2 is -O-, -S- or NR 9-;

R 3 is hydrogen, halogen, alkyl or alkoxy, or two radicals R 3 together with the carbon atom to which they are attached form a carbonyl group;

Y 1 is a bond or optionally substituted alkylene;
R^4 is hydrogen, alkyl, cycloalkylalkyl, halogenated alkyl, hydroxyalkyl, aminoalkyl, -CH_2CN, aryalkyl, optionally substituted cycloalkyl, -CHO, alky carbonyl, (halogenated alkyl)carbonyl, aralkylcarbonyl, alkoxy carbonyl, alkylaminocarbonyl, alkenyl, -C(=NH)NH_2, -C(=NH)NHCN, alkylsulfonyl, arylsulfonyl, amino, -NO or optionally substituted heterocycl; or

R^4 is optionally substituted alkylene that is bound to a carbon atom in Y^1;

R^4 is hydrogen, alkyl, halogenated alkyl, hydroxyalkyl, aminoalkyl, -CH_2CN, -CHO, alky carbonyl, (halogenated alkyl)carbonyl, aralkylcarbonyl, alkoxy carbonyl, aryl oxycarbonyl, alkylaminocarbonyl, alkenyl, -C(=NH)NH_2, -C(=NH)NHCN, alkylsulfonyl, arylsulfonyl, amino, -NO or heterocycl; or

R^4, R^4b together are optionally substituted alkylene, wherein one -CH_2- of alkylene may be replaced by an oxygen atom or -NR^0,;

X^2 is -0-, -NR^11a, -S-, >CR^12b or a bond;

X^3 is -0-, -NR^11b, -S-, >CR^13a or a bond;

R^5 is optionally substituted aryl, optionally substituted cycloalkyl or optionally substituted heterocycl;

R^7 is hydrogen or alkyl;

R^8 is hydrogen, alkyl, cycloalkyl, aminoalkyl, optionally substituted arylalkyl or heterocycl; or

R^8, R^1 together are alkylene;

R^9 is hydrogen, alkyl, cycloalkylalkyl, halogenated alkyl, hydroxyalkyl, aminoalkyl, -CH_2CN, aryalkyl, cycloalkyl, -CHO, alky carbonyl, (halogenated alkyl)carbonyl, aryl carbonyl, alkoxy carbonyl, aryloxycarbonyl, alkylaminocarbonyl, alkenyl, -C(=NH)NH_2, -C(=NH)NHCN, alkylsulfonyl, arylsulfonyl, amino, -NO or heterocycl;

R^10 is hydrogen or alkyl;

R^11a is hydrogen or alkyl;

R^11b is hydrogen or alkyl;
R\textsuperscript{12a} is hydrogen, optionally substituted alkyl, alkylaminoalkyl, dialkylaminoalkyl, heterocyclyl-alkyl, optionally substituted aryl or hydroxy;

5 R\textsuperscript{12b} is hydrogen or alkyl, or

R\textsuperscript{12a}, R\textsuperscript{12b} together with the carbon atom to which they are attached form a carbonyl or are optionally substituted alkenylene, wherein one -CH\textsubscript{2}- of alkenylene may be replaced by an oxygen atom or -NR\textsuperscript{id};

R\textsuperscript{13a} is hydrogen, optionally substituted alkyl, alkylaminoalkyl, dialkylaminoalkyl, heterocyclyl-alkyl, optionally substituted aryl or hydroxy;

15 R\textsuperscript{13b} is hydrogen or alkyl,

R\textsuperscript{13a}, R\textsuperscript{13b} together with the carbon atom to which they are attached form a carbonyl or are optionally substituted alkenylene, wherein one -CH\textsubscript{2}- of alkenylene may be replaced by an oxygen atom or -(CH\textsubscript{2})\textsuperscript{1};

R\textsuperscript{id} is hydrogen or alkyl; and

R\textsuperscript{id} is hydrogen or alkyl,

25 or a physiologically tolerated salt thereof.

Thus, the terms aminochromane, aminothiochromane and amino-1,2,3,4-tetrahydroquinoline derivatives are used herein to denote in particular aminochromanes (A\textsuperscript{2} is -0-) and aminothiochromanes (A\textsuperscript{2} is -S-) and 1,2,3,4-tetrahydroquinolines (A\textsuperscript{2} is -NR\textsuperscript{9}-) as well as fused tetrahydropyrans, tetrahydrothiopyrans and tetrahydropyridines wherein the benzene ring of the chromanes, thiochromanes and 1,2,3,4-tetrahydroquinolines is replaced by a 5- or 6-membered heterocyclic ring.

Said compounds of formula (I), i.e., the aminochromane, aminothiochromane and amino-1,2,3,4-tetrahydroquinoline derivatives of formula (I) and their physiologically tolerated salts, are glycine transporter inhibitors and thus useful as pharmaceuticals. Compounds of formula (I) combine high metabolic stability with high affinity. Compounds of formula (I) show favorable efflux properties which may lead to enhanced oral bioavailability and/or increased brain availability. Compounds of formula (I) combine high metabolic stability and high affinity with favorable efflux properties.

The present invention thus further relates to the compounds of formula (I) for use in therapy.
The present invention also relates to pharmaceutical compositions which comprise a carrier and a compound of formula (I).

In particular, said compounds, i.e., the aminochromane, aminothiochromane and amino-1,2,3,4-tetrahydroquinoline derivatives and their physiologically tolerated salts, are inhibitors of the glycine transporter GlyT1.

The present invention thus further relates to the compounds of formula (I) for use in inhibiting the glycine transporter GlyT1.

The present invention also relates to the use of the compounds of formula (I) in the manufacture of a medicament for inhibiting the glycine transporter GlyT1 and corresponding methods of inhibiting the glycine transporter GlyT1.

Glycine transport inhibitors and in particular inhibitors of the glycine transporter GlyT1 are known to be useful in treating a variety of neurologic and psychiatric disorders.

The present invention thus further relates to the compounds of formula (I) for use in treating a neurologic or psychiatric disorder.

The present invention further relates to the compounds of formula (I) for use in treating pain.

The present invention also relates to the use of the compounds of formula (I) in the manufacture of a medicament for treating neurologic or psychiatric disorder and corresponding methods of treating said disorders. The present invention also relates to the use of the compounds of formula (I) in the manufacture of a medicament for treating pain and corresponding methods of treating pain.

Detailed Description Of The Invention

Provided that the aminochromane, aminothiochromane and amino-1,2,3,4-tetrahydroquinoline derivatives of the formula (I) of a given constitution may exist in different spatial arrangements, for example if they possess one or more centers of asymmetry, polysubstituted rings or double bonds, or as different tautomers, it is also possible to use enantiomeric mixtures, in particular racemates, diastereomeric mixtures and tautomeric mixtures, preferably, however, the respective essentially pure enantiomers, diastereomers and tautomers of the compounds of formula (I) and/or of their salts.

According to one embodiment, an enantiomer of the compounds of the present invention has the following formula:
wherein $R_1$, $W$, $A_1$, $Q$, $Y$, $R_6$, $n_2$, $X_1$, $A$, $R_2$, $A_2$, $R_3$, $Y_1$, $R_4a$, $R_4b$, $X_2$, $X_3$, $R_5$ are as defined herein.

According to another embodiment, an enantiomer of the compounds of the present invention has the following formula:

wherein $R_1$, $W$, $A_1$, $Q$, $Y$, $R_6$, $n_2$, $X_1$, $A$, $R_2$, $A_2$, $R_3$, $Y_1$, $R_4a$, $R_4b$, $X_2$, $X_3$, $R_5$ are as defined herein.

According to one embodiment, an enantiomer of the compounds of the present invention has the following formula:
wherein \( R^1, W, A^1, Q, Y, R^6, n_1, n_2, X^1, A, R^2, A^2, R^3, Y^1, R^{4a}, R^{4b}, X^2, X^3, R^5 \) are as defined herein.

According to another embodiment, an enantiomer of the compounds of the present invention has the following formula:

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\[
\begin{array}{c}
\text{R}^1 \text{W} \text{A}^1 \text{Q} \text{Y} \\
\text{R}^2 \text{N}^1 \text{X}^1 \\
\text{A}^2 \text{R}^3 \text{Y}^1 \text{N} \text{R}^{4a} \\
\text{R}^{4b} \text{X}^2 \text{X}^3 \text{R}^5
\end{array}
\]
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wherein \( R^1, W, A^1, Q, Y, R^6, n_1, n_2, X^1, A, R^2, A^2, R^3, Y^1, R^{4a}, R^{4b}, X^2, X^3, R^5 \) are as defined herein.

The physiologically tolerated salts of the aminochromane, aminothiocromane and amino-1,2,3,4-tetrahydroquinoline derivatives of the formula (I) are especially acid addition salts with physiologically tolerated acids. Examples of suitable physiologically tolerated organic and inorganic acids are hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, \( \text{C}_1-\text{C}_6 \)-alkylsulfonic acids, such as methanesulfonic acid, cycloaliphatic sulfonic acids, such as \( \text{S}-(\text{+})-10\)-camphor sulfonic acid, aromatic sulfonic acids, such as benzenesulfonic acid and toluenesulfonic acid, di- and tricarboxylic acids and hydroxycarboxylic acids having 2 to 10 carbon atoms, such as oxalic acid, malonic acid, maleic acid, fumaric acid, lactic acid, tartaric acid, citric acid, glycolic acid, adipic acid and benzoic acid. Other utilizable acids are described, e.g., in Fortschrritte der Arzneimittelforschung [Advances in drug research], Volume 10, pages 224 ff, Birkhauser Verlag, Basel and Stuttgart, 1966. The physiologically tolerated salts of the aminochromane, aminothiocromane and amino-1,2,3,4-tetrahydroquinoline derivatives also include salts of a physiologically tolerated anion with aminochromane, aminothiocromane and amino-1,2,3,4-tetrahydroquinoline derivatives wherein one or more than one nitrogen atom is quaternized, e.g. with an alkyl residue (e.g. methyl or ethyl).

The present invention moreover relates to compounds of formula (I) as defined herein, wherein at least one of the atoms has been replaced by its stable, non-radioactive isotope (e.g., hydrogen by deuterium, \(^{13}\text{C} \) by \(^{15}\text{C} \), \(^{14}\text{N} \) by \(^{15}\text{N} \), \(^{16}\text{O} \) by \(^{18}\text{O} \) and preferably wherein at least one hydrogen atom has been replaced by a deuterium atom.

Of course, such compounds contain more of the respective isotope than this naturally occurs and thus is anyway present in the compounds (I).
Stable isotopes (e.g., deuterium, $^{13}$C, $^{15}$N, $^{18}$O) are nonradioactive isotopes which contain one or more additional neutron than the normally abundant isotope of the respective atom. Deuterated compounds have been used in pharmaceutical research to investigate the in vivo metabolic fate of the compounds by evaluation of the mechanism of action and metabolic pathway of the non-deuterated parent compound (Blake et al. J. Pharm. Sci. 64, 3, 367-391 (1975)). Such metabolic studies are important in the design of safe, effective therapeutic drugs, either because the in vivo active compound administered to the patient or because the metabolites produced from the parent compound prove to be toxic or carcinogenic (Foster et al., Advances in Drug Research Vol. 14, pp. 2-36, Academic Press, London, 1985; Kato et al., J. Labelled Comp. Radiopharmaceut., 36(10):927-932 (1995); Kushner et al., Can. J. Physiol. Pharmacol, 77, 79-88 (1999).

Incorporation of a heavy atom particularly substitution of deuterium for hydrogen, can give rise to an isotope effect that could alter the pharmacokinetics of the drug. This effect is usually insignificant if the label is placed at a metabolically inert position of the molecule.

Stable isotope labeling of a drug can alter its physico-chemical properties such as pKa and lipid solubility. These changes may influence the fate of the drug at different steps along its passage through the body. Absorption, distribution, metabolism or excretion can be changed. Absorption and distribution are processes that depend primarily on the molecular size and the lipophilicity of the substance. These effects and alterations can affect the pharmacodynamic response of the drug molecule if the isotopic substitution affects a region involved in a ligand-receptor interaction.

Drug metabolism can give rise to large isotopic effect if the breaking of a chemical bond to a deuterium atom is the rate limiting step in the process. While some of the physical properties of a stable isotope-labeled molecule are different from those of the unlabeled one, the chemical and biological properties are the same, with one important exception: because of the increased mass of the heavy isotope, any bond involving the heavy isotope and another atom will be stronger than the same bond between the light isotope and that atom. In any reaction in which the breaking of this bond is the rate limiting step, the reaction will proceed slower for the molecule with the heavy isotope due to "kinetic isotope effect". A reaction involving breaking a C–D bond can be up to 700 percent slower than a similar reaction involving breaking a C–H bond. If the C–D bond is not involved in any of the steps leading to the metabolite, there may not be any effect to alter the behavior of the drug. If a deuterium is placed at a site involved in the metabolism of a drug, an isotope effect will be observed only if breaking of the C–D bond is the rate limiting step. There is evidence to suggest that whenever cleavage of an aliphatic C–H bond occurs, usually by oxidation catalyzed by a mixed-function oxidase, replacement of the hydrogen by deuterium will lead to observable isotope effect. It is also important to understand that the incorporation of deuterium at the site of metabolism slows its rate to the point where another metabolite produced by attack at a carbon atom not substituted by deuterium becomes the major pathway a process called "metabolic switching".
Deuterium tracers, such as deuterium-labeled drugs and doses, in some cases repeatedly, of thousands of milligrams of deuterated water, are also used in healthy humans of all ages, including neonates and pregnant women, without reported incident (e.g. Pons G and Rey E, Pediatrics 1999 104: 633; Coward W A et al., Lancet 1979 7: 13; Schwarzen H P, Control. Clin. Trials 1984 5(4 Suppl): 573; Rodewald L E et al., J. Pediatr. 1989 114: 885; Butte N F et al. Br. J. Nutr. 1991 65: 3; Mallesham B e t al., Org Lett, 5(7), 963 (2003); PCT publications has been observed; for example, in the metabolism of compounds of this invention poses no health risk.

The weight percentage of hydrogen in a mammal (approximately 9%) and natural abundance of deuterium (approximately 0.015%) indicates that a 70 kg human normally contains nearly a gram of deuterium. Furthermore, replacement of up to about 15% of normal hydrogen with deuterium has been effected and maintained for a period of days to weeks in mammals, including rodents and dogs, with minimal observed adverse effects (Czajka D M and Finkel A J, Ann. N.Y. Acad. Sci. 1960 84: 770; Thomson J F, Ann. New York Acad. Sci 1960 84: 736; Czajka D M et al., Am. J. Physiol. 1961 201: 357). Higher deuterium concentrations, usually in excess of 20%, can be toxic in animals. However, acute replacement of as high as 15%>23%> of the hydrogen in humans' fluids with deuterium was found not to cause toxicity (Blagojevic N et al. in "Dosimetry & Treatment Planning for Neutron Capture Therapy", Zamenhof R., Solares G and Harling O Eds. 1994. Advanced Medical Publishing, Madison Wis. pp.125-134; Diabetes Metab. 23: 251 (1997)).

Increasing the amount of deuterium present in a compound above its natural abundance is called enrichment or deuterium- enrichment. Examples of the amount of enrichment include from about 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 21, 25, 29, 33, 37, 42, 46, 50, 54, 58, 63, 67, 71, 75, 79, 84, 88, 92, 96, to about 100 mol %.

The hydrogens present on a particular organic compound have different capacities for exchange with deuterium. Certain hydrogen atoms are easily exchangeable under physiological conditions and, if replaced by deuterium atoms, it is expected that they will readily exchange for protons after administration to a patient. Certain hydrogen atoms may be exchanged for deuterium atoms by the action of a deuteric acid such as D₂SO₄/D₂O. Alternatively, deuterium atoms may be incorporated in various combinations during the synthesis of compounds of the invention. Certain hydrogen atoms are not easily exchangeable for deuterium atoms. However, deuterium atoms at the remaining positions may be incorporated by the use of deuterated starting materials or intermediates during the construction of compounds of the invention.

Deuterated and deuterium- enriched compounds of the invention can be prepared by using known methods described in the literature. Such methods can be carried out utilizing corresponding deuterated or optionally, other isotope-containing reagents and/or intermediates to synthesize the compounds delineated herein, or invoking standard synthetic protocols known in the art for introducing isotopic atoms to a chemical structure. Relevant procedures and intermediates are disclosed, for instance in Lizondo, J et al., Drugs Fut, 21(11), 1116 (1996); Brickner, S J et al, J Med Chem, 39(3), 673 (1996); Mallesham, B et al., Org Lett, 5(7), 963 (2003); PCT publications
The organic moieties mentioned in the above definitions of the variables are - like the term halogen - collective terms for individual listings of the individual group members. The prefix \( C_{\text{H}} \) indicates in each case the possible number of carbon atoms in the group. The prefix \( M_{\text{H}} \) indicates in each case the possible number of ring forming atoms (ring members) in the group.

Unless indicated otherwise, the term "substituted" means that a radical is substituted with 1, 2 or 3, especially 1, substituent which, according to a particular embodiment of the invention, are independently selected from the group consisting of halogen, \( C_{1-4} \) alkyl, \( C_{3-6} \) -aryl-C\( C_{4} \)-alkyl, halogenated-C\( C_{4} \)-alkyl, hydroxy-C\( C_{4} \)-alkyl, hydroxy-(halogenated \( C_{4} \)-alkyl), \( C_{1-4} \)-alkoxy-C\( C_{4} \)-alkyl, amino-C\( C_{4} \)-alkyl, \( C_{3-6} \)-heterocyclyl-C\( C_{4} \)-alkyl, \( C_{3-7} \)-cycloalkyl, \( C_{2-4} \)-alkenyl, \( C_{3-4} \)-alkylaminocarbonyl, \( C_{1-4} \)-alkoxycarbonyl, \( C_{1-4} \)-alkylamino, \( C_{1-4} \)-alkoxy, oxo (=\( \text{O} \)), \( C_{1-4} \)-alkoxy, halogenated-C\( C_{4} \)-alkoxy, \( C_{3-7} \)-cycloalkoxy, carboxy-C\( C_{4} \)-alkoxy, \( C_{6-12} \)-aryl-C\( C_{4} \)-alkoxy, \( C_{6-12} \)-aryl-C\( C_{4} \)-alkylthio, \( C_{1-4} \)-alkylsulfonyl, \( C_{1-4} \)-alkylaminosulfonyl, \( C_{3-6} \)-arylsulfonyl, \( C_{3-6} \)-aminosulfonyl, \( C_{1-4} \)-alkylaminosulfonyl, \( C_{1-4} \)-alkoxycarbonylamino, \( C_{1-4} \)-arylamino, \( C_{1-4} \)-alkylamino, \( C_{1-4} \)-alkylaminocarbonyl, \( C_{1-4} \)-arylcyanocarbonyl, \( C_{1-4} \)-arylaminocarbonyl, \( C_{1-4} \)-arylsulfonylamino, \( C_{6-12} \)-heterocyclylsulfonylamino, and \( C_{1-4} \)-heterocyclylsulfonylamino.

The term halogen denotes in each case fluorine, bromine, chlorine or iodine, in particular fluorine or chlorine.

\( C_{1-4} \)-Alkyl is a straight-chain or branched alkyl group having from 1 to 4 carbon atoms. Examples of an alkyl group are methyl, \( C_{2-4} \)-alkyl such as ethyl, n-propyl, iso-propyl, n-butyl, 2-butyl, iso-butyl or tert-butyl. \( C_{1-4} \)-Alkyl is methyl or ethyl, \( C_{1-3} \)-alkyl is additionally n-propyl or isopropyl.

\( C_{1-6} \)-Alkyl is a straight-chain or branched alkyl group having from 1 to 6 carbon atoms. Examples include methyl, \( C_{2-4} \)-alkyl as mentioned herein and also pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-
ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl and 1-ethyl-2-methylpropyl.

Halogenated Ci-C6-alkyl is a straight-chain or branched alkyl group having 1 to 6 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by 1, 2, 3, 4 or a corresponding number of identical or different halogen atoms, such as in halogenomethyl, dihalogenomethyl, trihalogenomethyl, (R)-1-halogenoethyl, (S)-1-halogenoethyl, 2-halogenoethyl, 1,1-dihalogenoethyl, 2,2-dihalogenoethyl, 2,2,2-trihalogenoethyl, (R)-1-halogenopropyl, (S)-1-halogenopropyl, 2-halogenopropyl, 3-halogenopropyl, 1,1-dihalogenopropyl, 2,2-dihalogenopropyl, 3,3-dihalogenopropyl, 3,3,3-trihalogenopropyl, (R)-2-halogeno-1-methylethyl, (S)-2-halogeno-1-methylethyl, (R)-2,2-dihalogeno-1-methylethyl, (S)-2,2-dihalogeno-1-methylethyl, (R)-1,2-dihalogeno-1-methylethyl, (S)-1,2-dihalogeno-1-methylethyl, (R)-2,2,2-trihalogeno-1-methylethyl, (S)-2,2,2-trihalogeno-1-methylethyl, 2-halogeno-1-(halogenomethyl)ethyl, 1-(halogenomethyl)-2,2-dihalogenoethyl, (R)-1-halogenobutyl, (S)-1-halogenobutyl, 2-halogenobutyl, 3-halogenobutyl, 4-halogenobutyl, 1,1-dihalogenobutyl, 2,2-dihalogenobutyl, 3,3-dihalogenobutyl, 4,4-dihalogenobutyl, 4,4,4-trihalogenobutyl, etc. Particular examples include the fluorinated Ci-Ce alkyl groups as defined, such as trifluoromethyl.

C3-C62 -Cycloalkyl-Ci-C4-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in particular 1 or two carbon atoms, wherein one hydrogen atom is replaced by a cycloaliphatic radical having from 3 to 12 carbon atoms such as in cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl.

C6-C2 -Aryl-Ci-C4-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in particular 1 or two carbon atoms, wherein one hydrogen atom is replaced by C6-C2 -aryl, such as in benzyl.

Hydroxy-C1-C4-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, wherein one or two hydrogen atoms are replaced by one or two hydroxyl groups, such as in hydroxymethyl, (R)-1-hydroxyethyl, (S)-1-hydroxyethyl, 2-hydroxyethyl, (R)-1-hydroxypropyl, (S)-1-hydroxypropyl, 2-hydroxypropyl, 3-hydroxypropyl, (R)-2-hydroxy-1-methylethyl, (S)-2-hydroxy-1-methylethyl, 2-hydroxy-1-(hydroxymethyl) ethyl, (R)-1-hydroxybutyl, (S)-1-hydroxybutyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl.

Ci-C6-Alkoxy-Ci-C4-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, wherein one or two hydrogen atoms are replaced by one or two alkoxy groups having 1 to 6, preferably 1 to 4, in particular 1 or 2 carbon atoms, such as in methoxymethyl, (R)-1-methoxyethyl, (S)-1-methoxyethyl, 2-methoxyethyl, (R)-1-methoxypropyl, (S)-1-methoxypropyl, 2-methoxypropyl, 3-methoxypropyl,
(R)-2-methoxy-1-methylethyl, (S)-2-methoxy-1-methylethyl, 2-methoxy-1-(methoxymethyl)ethyl, (R)-1-methoxybutyl, (S)-1-methoxybutyl, 2-methoxybutyl, 3-methoxybutyl, 4-methoxybutyl, ethoxyethyl, (R)-l-ethoxyethyl, (S)-l-ethoxyethyl, 2-ethoxyethyl, (R)-l-ethoxypropyl, (S)-l-ethoxypropyl, 2-ethoxypropyl, 3-ethoxypropyl, (R)-2-ethoxy-1-methylethyl, (S)-2-ethoxy-1-methylethyl, 2-ethoxy-1-(ethoxymethyl)ethyl, (R)-l-ethoxybutyl, (S)-l-ethoxybutyl, 2-ethoxybutyl, 3-ethoxybutyl, 4-ethoxybutyl.

Amino-C₁-C₄-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in particular 1 or two carbon atoms, wherein one hydrogen atom is replaced by an amino group, such as in aminomethyl, 2-aminoethyl.

Ci-C₆-Alkylamino-Ci-C₄-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in particular 1 or two carbon atoms, wherein one hydrogen atom is replaced by a Ci-C₆-alkylamino group, in particular by a Ci-C₄-alkylamino group, such as in methylaminomethyl, ethylaminomethyl, n-propylaminomethyl, iso-propylaminomethyl, n-butylaminomethyl, 2-butylaminomethyl, iso-butylaminomethyl or tert-butylaminomethyl.

Di-Ci-C₆-Alkylamino-Ci-C₄-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in particular 1 or two carbon atoms, wherein one hydrogen atom is replaced by a di-Ci-C₆-Alkylamino group, in particular by a di-Ci-C₄-alkylamino group, such as in dimethylaminomethyl.

Ci-C₆-Alkylcarbonylamino-Ci-C₄-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in particular 1 or two carbon atoms, wherein one hydrogen atom is replaced by a Ci-C₆-alkylcarbonylamino group, in particular by a Ci-C₄-alkylcarbonylamino group, such as in methylcarbonylaminoethyl, ethylcarbonylaminoethyl, n-propylcarbonylaminoethyl, iso-propylcarbonylaminoethyl, n-butylcarbonylaminoethyl, 2-butylcarbonylaminoethyl, iso-butylcarbonylaminoethyl or tert-butylcarbonylaminoethyl.

Ci-C₆-Alkaminocarbonylamino-Ci-C₄-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in particular 1 or two carbon atoms, wherein one hydrogen atom is replaced by a Ci-C₆-alkaminocarbonylamino group, in particular by a Ci-C₄-alkaminocarbonylamino group, such as in methylaminocarbonylaminoethyl, ethylaminocarbonylaminoethyl, n-propylaminocarbonylaminoethyl, iso-propylaminocarbonylaminoethyl, n-butylaminocarbonylaminoethyl, 2-butylaminocarbonylaminoethyl, iso-butylaminocarbonylaminoethyl or tert-butylaminocarbonylaminoethyl.

Di-Ci-C₆-alkaminocarbonylamino-Ci-C₄-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in par-
ticular 1 or two carbon atoms, wherein one hydrogen atom is replaced by a di-Ci-C6-alkylaminocarbonylamino group, in particular by a di-Ci-C4-alkylaminocarbonylamino group, such as in dimethylaminocarbonylaminomethyl, dimethylaminocarbonylaminoethyl, dimethylaminocarbonylaminon-propyl.

5

Ci-C6-Alkylsulfonylamino-Ci-C4-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in particular 1 or two carbon atoms, wherein one hydrogen atom is replaced by a Ci-C6-alkylsulfonylamino group, in particular by a Ci-C4-alkylsulfonylamino group, such as in methylsulfonylaminomethyl, ethylsulfonylaminomethyl, n-propylsulfonylaminomethyl, iso-propylsulfonylaminomethyl, n-butylsulfonylaminomethyl, 2-butylsulfonylaminomethyl, iso-butylsulfonylaminomethyl or tert-butylsulfonylaminomethyl.

10

(C6-C12)-Aryl-Ci-C6-alkylamino-Ci-C4 alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in particular 1 or two carbon atoms, wherein one hydrogen atom is replaced by a (C6-C12)-aryl-Ci-C6-alkylamino group, in particular a (C6-C12)-aryl-Ci-C2-alkylamino group, such as inbenzylaminomethyl.

15

M3-Mi2-Heterocycl-Ci-C4-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in particular 1 or two carbon atoms, wherein one hydrogen atom is replaced by M3-Mi2-heterocycl, such as in N-pyrroldinylmethyl, N-piperidinylmethyl, N-morpholinylmethyl.

20

C3-C12-Cycloalkyl is a cycloaliphatic radical having from 3 to 12 carbon atoms. In particular, 3 to 6 carbon atoms form the cyclic structure, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The cyclic structure may be unsubstituted or may carry 1, 2, 3 or 4 Ci-C4 alkyl radicals, preferably one or more methyl radicals.

25

Carbonyl is >C=O.

30

Ci-C6-Alkylcarbonyl is a radical of the formula R-C(O)-, wherein R is an alkyl radical having from 1 to 6, preferably from 1 to 4, in particular 1 or 2 carbon atoms as defined herein. Examples include acetyl, propionyl, n-butyryl, 2-methylpropionyl, pivaloyl.

35

Halogenated Ci-C6-alkylcarbonyl is Ci-C6-alkylcarbonyl as defined herein, wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by 1, 2, 3, 4 or a corresponding number of identical or different halogen atoms. Examples include fluoroethylcarbonyl, difluoroethylcarbonyl, trifluoroethylcarbonyl. Further examples are 1,1,1-trifluoroeth-2-y carbonyl, 1,1,1-trifluoroprop-3-y carbonyl.
C6-C12 -Arylcarbonyl is a radical of the formula R-C(O)-, wherein R is an aryl radical having from 6 to 12 carbon atoms as defined herein. Examples include benzyol.

C1-C6 -Alkoxy carbonyl is a radical of the formula R-O-C(O)-, wherein R is an alkyl radical having from 1 to 6, preferably from 1 to 4, in particular 1 or 2 carbon atoms as defined herein. Examples include methoxycarbonyl and tert-butyloxycarbonyl.

Halogenated C1-C6 -alkoxy carbonyl is a C1-C6 -alkoxy carbonyl as defined herein, wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by 1, 2, 3, 4 or a corresponding number of identical or different halogen atoms.

C6-C12 -Aryloxy carbonyl is a radical of the formula R-O-C(O)-, wherein R is an aryl radical having from 6 to 12 carbon atoms as defined herein. Examples include phenoxy carbonyl.

Cyano is -C≡N.

Aminocarbonyl is NH₂C(O)-.

C1-C6 -Arylaminocarbonyl is a radical of the formula R-NH-C(O)-, wherein R is an aryl radical having from 1 to 6, preferably from 1 to 4, in particular 1 or 2 carbon atoms as defined herein. Examples include methylaminocarbonyl.

(Halogenated C1-C4 -alkyl)aminocarbonyl is a C1-C4 -alkylaminocarbonyl as defined herein, wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by 1, 2, 3, 4 or a corresponding number of identical or different hydrogen atoms.

C6-C12 -Arylaminocarbonyl is a radical of the formula R-NH-C(O)-, wherein R is an aryl radical having from 6 to 12 carbon atoms as defined herein. Examples include phenylaminocarbonyl.

C2-C6 -Alkenyl is a singly unsaturated hydrocarbon radical having 2, 3, 4, 5 or 6 carbon atoms, e.g. vinyl, allyl (2-propen-1-yl), 1-propen-1-yl, 2-propen-2-yl, methallyl(2-methylprop-2-en-1-yl) and the like. C₃-C₅-Alkenyl is, in particular, allyl, 1-methylprop-2-en-1-yl, 2-buten-1-yl, 3-buten-1-yl, methallyl, 2-penten-1-yl, 3-penten-1-yl, 4-penten-1-yl, 1-methylbut-2-en-1-yl or 2-ethylprop-2-en-1-yl.

C2-C6 -Alkynyl is a singly unsaturated hydrocarbon radical having 2, 3, 4, 5 or 6 carbon atoms, e.g. ethynyl, 2-propyn-1-yl, 1-propyn-1-yl, 2-propyn-2-yl and the like. C₃-C₅-Alkynyl is, in particular, 2-propyn-1-yl, 2-butyn-1-yl, 3-butyn-1-yl, 2-pentyn-1-yl, 3-pentyn-1-yl, 4-pentyn-1-yl.

C1-C4 -Alkylene is straight-chain or branched alkylene group having from 1 to 4 carbon atoms. Examples include methylene and ethylene. A further example is propylene.
C2-C6 -Alkylene is straight-chain or branched alkylene group having from 2 to 6 carbon atoms. Examples include ethylene. A further example is propylene.

C2-C4 - Alkenylene is straight-chain or branched alkenylene group having from 2 to 4 carbon atoms.

C2-C4 - Alkynylene is straight-chain or branched alkynylene group having from 2 to 4 carbon atoms. Examples include propynylene.

C6-C2 - Aryl is a 6- to 12-membered, in particular 6- to 10-membered, aromatic cyclic radical. Examples include phenyl and naphthyl.

C3-C2 - Arylene is an aryl diradical. Examples include phen-l,4-ylene and phen-l,3-ylene.

Hydroxy is -OH.

C1-C6 - Alkoxyl is a radical of the formula R-O-, wherein R is a straight-chain or branched alkyl group having from 1 to 6, in particular 1 to 4 carbon atoms. Examples include methoxy, ethoxy, n-propoxy, isopropanoxy, n-butoxy, 2-butoxy, iso-butoxy (2-methylpropoxy), tert.-butoxy pentyloxy, 1-methylbutoxy, 2-methylbutoxy, 3-methylbutoxy, 2,2-dimethylpropoxy, 1-ethylpropoxy, hexyloxy, 1,1-dimethylpropoxy, 1,2-dimethylpropoxy, 1-methylpentyloxy, 2-methylpentyloxy, 3-methylpentyloxy, 4-methylpentyloxy, 1,1-dimethylbutyloxy, 1,2-dimethylbutyloxy, 1,3-dimethylbutyloxy, 2,2-dimethylbutyloxy, 2,3-dimethylbutyloxy, 3,3-dimethylbutyloxy, 1-ethylbutyloxy, 2-ethylbutyloxy, 1,1,2-trimethylpropoxy, 1,2,2-trimethylpropoxy, 1-ethyl-1-methyloxy and 1-ethyl-2-methyloxy.

Halogenated C1-C6 -alkoxy is a straight-chain or branched alkoxy group having from 1 to 6, preferably from 1 to 4, in particular 1 or 2 carbon atoms, wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by 1, 2, 3, 4 or a corresponding number of identical or different halogen atoms, such as in halogenomethoxy, dihalogenomethoxy, trihalogenomethoxy, (R)-1-halogenoethoxy, (S)-1-halogenoethoxy, 2-halogenoethoxy, 1,1-dihalogenoethoxy, 2,2-dihalogenoethoxy, 2,2,2-trihalogenoethoxy, (R)-1-halogenopropoxy, (S)-1-halogenopropoxy, 2-halogenopropoxy, 3-halogenopropoxy, 1,1-dihalogenopropoxy, 2,2-dihalogenopropoxy, 3,3-dihalogenopropoxy, 3,3,3-trihalogenopropoxy, (R)-2-halogeno-l-methylethoxy, (S)-2-halogeno-l-methylethoxy, (R)-2,2-di-halogeno-l-methylethoxy, (S)-2,2-di-halogeno-l-methylethoxy, (R)-1,2-dihalogeno-1-methylethoxy, (S)-1,2-dihalogeno-1-methylethoxy, (R)-2,2,2-trihalogeno-1-methylethoxy, (S)-2,2,2-trihalogeno-1-methylethoxy, 2-halogeno-l-(halogenomethyl)ethoxy, 1-(halogenomethyl)-2,2-dihalogenoethoxy, (R)-l-halogenobutoxy, (S)-l-halogenobutoxy, 2-halogenobutoxy, 3-halogenobutoxy, 4-halogenobutoxy, 1,1-dihalogenobutoxy, 2,2-dihalogenobutoxy, 3,3-dihalogenobutoxy, 4,4-dihalogenobutoxy, 4,4,4-trihalogenobutoxy, etc.

Particular examples include the fluorinated C1-C4 alkoxy groups as defined, such as trifluoromethoxy.
C_{1-C6} -Hydroxyalkoxy is an alkoxy radical having from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein, wherein one or two hydrogen atoms are replaced by hydroxy. Examples include 2-hydroxyethoxy, 3-hydroxypropoxy, 2-hydroxypropoxy, 1-methyl-2-hydroxyethoxy and the like.

C_{1-C6} -Alkoxy -C_{1-C4} -alkoxy is an alkoxy radical having from 1 to 4 carbon atoms, preferably 1 or 2 carbon atoms as defined herein, wherein one or two hydrogen atoms are replaced by one or two alkoxy radicals having from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein. Examples include methoxymethoxy, 2-methoxyethoxy, 1-methoxyethoxy, 3-methoxypropoxy, 2-methoxypropoxy, 1-methyl-1-methoxyethoxy, ethoxymethoxy, 2-ethoxyethoxy, 1-ethoxyethoxy, 3-ethoxypropoxy, 2-ethoxypropoxy, 1-methyl-1-ethoxyethoxy and the like.

Amino -C_{1-C4}-alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by an amino group. Examples include 2-aminoethoxy.

C_{1-C6} -Alkylamino -C_{1-C4} -alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by an alkylamino group having from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein. Examples include methylinomethoxy, ethylaminomethoxy, n-propylaminomethoxy, iso-propylaminomethoxy, n-butylaminomethoxy, 2-butylaminomethoxy, iso-butylaminomethoxy, tert-butylaminomethoxy, 2-(methylamino)ethoxy, 2-(ethylamino)ethoxy, 2-(n-propylamino)ethoxy, 2-(iso-propylamino)ethoxy, 2-(n-butylamino)ethoxy, 2-(2-buty lamino)ethoxy, 2-(iso-butylamino)ethoxy, 2-(tert-butylamino)ethoxy.

Di-C_{1-C6} -alkylamino -C_{1-C4} -alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by a di-alkylamino group having from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein. Examples include dimethylaminomethoxy, diethylaminomethoxy, N-methyl-N-ethylaminoethoxy, 2-(dimethylamino)ethoxy, 2-(diethylamino)ethoxy, 2-(N-methyl-N-ethylamino)ethoxy.

C_{1-C6} -Alkylcarbonylamino -C_{1-C4} -alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by an alkylcarbonylamino group wherein the alkyl group has from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein. Examples include methylcarbonylaminomethoxy, ethylcarbonylaminomethoxy, n-propylcarbonylaminomethoxy, iso-propylcarbonylaminomethoxy, 2-butylcarbonylaminomethoxy, iso-butylcarbonylaminomethoxy, tert-butylcarbonylaminomethoxy, 2-(methylcarbonylamino)ethoxy, 2-(ethylcarbonylamino)ethoxy, 2-(n-propylcarbonylamino)ethoxy, 2-(iso-propylcarbonylamino)ethoxy, 2-(n-butylcarbonylamino)ethoxy, 2-(2-buty lacarbonylamino)ethoxy, 2-(iso-butylcarbonylamino)ethoxy, 2-(tert-butylcarbonylamino)ethoxy.
C₆-C₂ -Arylcarbonylamino -C₁-C₄ -alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by a C₆-C₁₂ arylcarbonylamino group as defined herein. Examples include 2-(benzoylamino)ethoxy.

C₁-C₆ -Alkoxycarbonylamino -C₁-C₄ -alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by an alkoxy carbonylamino group wherein the alkoxy group has from 1 to 4, preferably from 1 to 4 carbon atoms as defined herein. Examples include methoxycarbonylaminomethoxy, ethoxycarbonylaminomethoxy, n-propoxycarbonylaminomethoxy, iso-propoxycarbonylaminomethoxy, n-butoxycarbonylaminomethoxy, 2-butoxycarbonylaminomethoxy, iso-butoxycarbonylaminomethoxy, tert-butoxycarbonylaminomethoxy, 2-(methoxycarbonylamino)ethoxy, 2-(ethoxycarbonylamino)ethoxy, 2-(n-propoxycarbonylamino)ethoxy, 2-(iso-propoxycarbonylamino)ethoxy, 2-(n-butoxycarbonylamino)ethoxy, 2-(2-butoxycarbonylamino)ethoxy, 2-(iso-butoxycarbonylamino)ethoxy, 2-(tert-butoxycarbonylamino)ethoxy.

C₂-C₆ -Alkenyloxy is a radical of the formula R-Ø, wherein R is a straight-chain or branched alkenyl group having from 2 to 6, in particular 2 to 4 carbon atoms. Examples include vinyloxy, allyloxy (2-propen-1-yloxy), 1-propen-1-yloxy, 2-propen-2-yloxy, methallyloxy (2-methylprop-2-en-1-yloxy) and the like, C₃-C₅-Alkenyloxy is, in particular, allyloxy, 1-methylprop-2-en-1-yloxy, 2-buten-1-yloxy, 3-buten-1-yloxy, methallyloxy, 2-penten-1-yloxy, 3-penten-1-yloxy, 4-penten-1-yloxy, 1-methylbut-2-en-1-yloxy or 2-ethylprop-2-en-1-yloxy.

C₆-C₂ -Aryl-C₁-C₄ -alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by a C₆-C₂ -aryl group as defined herein. Examples include benzylloxy.

C₁-C₆ -Alkylsulfonylamino -C₁-C₄ -alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by an alkylsulfonylamino group having from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein. Examples include 2-(methylsulfonylamino)ethoxy, 2-(ethylsulfonylamino)ethoxy, 2-[(2-methylpropyl)sulfonylamino]ethoxy.

(Halogenated C₁-C₆ -alkyl)sulfonylamino -C₁-C₄ -alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by an alkylsulfonylamino group having from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein, wherein the alkyl group is halogenated. Examples include 2-(trifluoromethylsulfonylamino)ethoxy.

C₆-C₂ -Arylsulfonylamino -C₁-C₄ -alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by a C₆-C₁₂ arylsulfonylamino group as defined herein. Examples include 2-(phenylsulfonylamino)ethoxy, 2-(naphthylsulfonylamino)ethoxy.
(C₆-C₁₂ -Aryl-C₆-alkyl)sulfonylamino-C₁-C₄-alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by a (C₆-C₁₂ -aryl-C₆-alkyl)sulfonylamino group, preferably by a (C₆-C₁₂ -aryl-C₂-alkyl)sulfonylamino group. Examples include 2-(benzylsulfonylamino)ethoxy.

M₃-M₂ -Heterocyclylsulfonylamino-C₁-C₄-alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by a M₃-M₂ heterocyclylsulfonylamino group as defined herein. Examples include 2-(pyridin-3-yl-sulfonylamino)ethoxy.

M₃-M₂ -Heterocyclyl-C₁-C₄-alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by a M₃-M₂ heterocyclyl group as defined herein. Examples include 2-(N-pyrrolidinyl)ethoxy, 2-(N-morpholinyl)ethoxy and 2-(N-imidazolyl)ethoxy.

C₁-C₂ -Alkylenedioxo is a radical of the formula -O-R-O-, wherein R is a straight-chain or branched alkylene group having from 1 or 2 carbon atoms as defined herein. Examples include methylenedioxo.

C₆-C₁₂ -Aryloxy is a radical of the formula R-0-, wherein R is an aryl group having from 6 to 12, in particular 6 carbon atoms as defined herein. Examples include phenoxy.

M₃-M₁₂ -Heterocyclyloxy is a radical of the formula R-0-, wherein R is a M₃-M₁₂ heterocyclyl group having from 3 to 12, in particular from 3 to 7 ring forming atoms (ring members) as defined herein. Examples include pyridin-2-yl-oxy.

C₁-C₆ -Alkylthio is a radical of the formula R-S-, wherein R is an alkyl radical having from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein. Examples include methylthio, ethylthio, propylthio, butylthio, pentylthio, 1-methylbutylthio, 2-methylbutylthio, 3-methylbutylthio, 2,2-dimethylpropylthio, 1-ethylpropylthio, hexylthio, 1,1-dimethylpropylthio, 1,2-dimethylpropylthio, 1-methylpentylthio, 2-methylpentylthio, 3-methylpentylthio, 4-methylpentylthio, 1,1-dimethylbutylthio, 1,2-dimethylbutylthio, 1,3-dimethylbutylthio, 2,2-dimethylbutylthio, 2,3-dimethylbutylthio, 3,3-dimethylbutylthio, 1-ethylbutylthio, 2-ethylbutylthio, 1,1,2-trimethylpropylthio, 1,2,2-trimethylpropylthio, 1-ethyl-1-methylpropyl and 1-ethyl-2-methylpropyl.

Halogenated C₁-C₆ -alkylthio is a radical of the formula R-S-, wherein R is a halogenated alkyl radical having from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein. Examples include halogenomethylthio, dihalogenomethylthio, trihalogenomethylthio, (R)-1-halogenoethylthio, (S)-1-halogenoethylthio, 2-halogenoethylthio, 1,1-dihalogenoethylthio, 2,2-dihalogenoethylthio, 2,2,2-trihalogenoethylthio, (R)-1-halogenopropylthio, (S)-1-halogenopropylthio, 2-halogenopro-
pylthio, 3-halogenopropylthio, 1,1-dihalogenopropylthio, 2,2-dihalogenopropylthio, 3,3-dihalo-
genopropylthio, 3,3,3-trihalogenopropylthio, (R)-2-halogeno-1-methylethylthio, (S)-2-halogeno-1-
methylethylthio, (R)-2,2-dihalogeno-1-methylethylthio, (S)-2,2-dihalogeno-1-methylethylthio, (R)-
1,2-dihalogeno-1-methylethylthio, (S)-1,2-dihalogeno-1-methylethylthio, (R)-2,2,2-trihalogeno-1-
methylethylthio, (S)-2,2,2-trihalogeno-1-methylethylthio, 2-halogeno-1-(halogenomethyl)ethylthio,
1-(dihalogenomethyl)-2,2-dihalogenoethylthio, (R)-1-halogenobutylthio, (S)-1-halogenobutylthio,
2-halogenobutylthio, 3-halogenobutylthio, 4-halogenobutylthio, 1,1-dihalogenobutylthio, 2,2-
dihalogenobutylthio, 3,3-dihalogenobutylthio, 4,4-dihalogenobutylthio, 4,4,4-trihalogenobutylthio,
etc. Particular examples include the fluorinated C1-C4 alkylthio groups as defined, such as trifluo-
romethylthio.

C1-C6 -Alkylsulfinyl is a radical of the formula R-S(O)-, wherein R is an alkyl radical having from 1
to 6, preferably from 1 to 4 carbon atoms as defined herein. Examples include methylsulfinyl,
ethylsulfinyl, propylsulfinyl, butylsulfinyl, pentylsulfinyl, 1-methylbutylsulfinyl,
2-methylbutylsulfinyl, 3-methylbutylsulfinyl, 2,2-dimethylpropylsulfinyl, 1-ethylpropylsulfinyl,
hexylsulfinyl, 1,1-dimethylpropylsulfinyl, 1,2-dimethylpropylsulfinyl, 1-methylpentylsulfinyl, 2-
methylpentylsulfinyl, 3-methylpentylsulfinyl, 4-methylpentylsulfinyl, 1,1-dimethylbutylsulfinyl,
1,2-dimethylbutylsulfinyl, 1,3-dimethylbutylsulfinyl, 2,2-dimethylbutylsulfinyl, 2,3-
dimethylbutylsulfinyl, 3,3-dimethylbutylsulfinyl, 1-ethylbutylsulfinyl, 2-ethylbutylsulfinyl, 1,1,2-
trimethylpropylsulfinyl, 1,2,2-trimethylpropylsulfinyl, 1-ethyl-1-methylpropyl and 1-ethyl-2-
methylypropyl.

C1-C6 -Alkylsulfonyl is a radical of the formula R-S(O)2-, wherein R is an alkyl radical having from 1
to 6, preferably from 1 to 4 carbon atoms as defined herein. Examples include methylsulfonyl,
ethylsulfonyl, propylsulfonyl, butylsulfonyl, pentylsulfonyl, 1-methylbutylsulfonyl,
2-methylbutylsulfonyl, 3-methylbutylsulfonyl, 2,2-dimethylpropylsulfonyl, 1-ethylpropylsulfonyl,
hexylsulfonyl, 1,1-dimethylpropylsulfonyl, 1,2-dimethylpropylsulfonyl, 1-methylpentylsulfonyl, 2-
methylpentylsulfonyl, 3-methylpentylsulfonyl, 4-methylpentylsulfonyl, 1,1-dimethylbutylsulfonyl,
1,2-dimethylbutylsulfonyl, 1,3-dimethylbutylsulfonyl, 2,2-dimethylbutylsulfonyl, 2,3-
dimethylbutylsulfonyl, 3,3-dimethylbutylsulfonyl, 1-ethylbutylsulfonyl, 2-ethylbutylsulfonyl, 1,1,2-
trimethylpropylsulfonyl, 1,2,2-trimethylpropylsulfonyl, 1-ethyl-1-methylpropyl and 1-ethyl-2-
methylypropyl.

(Halogenated C1-C6 -alkyl)sulfonyl is a C1-C6 -alkylsulfonyl as defined herein, wherein at least one,
e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by 1, 2, 3, 4 or a corresponding number of
identical or different halogen atoms.

C6-C2 -Arylsulfonyl is a radical of the formula R-S(O)2-, wherein R is an aryl radical having from 6
to 12 carbon atoms as defined herein. Examples include phenylsulfonyl.
(C6-C12 -Aryl-C4-alkyl)sulfonyl is a radical of the formula R-S(0)2-, wherein R is a C6-C12 -aryl-C1-C4-alkyl radical, in particular a C6-C12 -aryl-C2-alkyl radical as defined herein. Examples include benzylsulfonyl.

5 M1-M2 -Heterocyclylsulfonyl is a radical of the formula R-S(0)2-, wherein R is M1-M2 -heterocyclyl as defined herein.

Aminosulfonyl is NH2-S(0)2-.

10 C1-C6 -Alkylaminosulfonyl is a radical of the formula R-NH-S(0)2- wherein R is an alkyl radical having from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein. Examples include methylaminosulfonyl, ethylaminosulfonyl, n-propylaminosulfonyl, iso-propylaminosulfonyl, n-butylaminosulfonyl, 2-butylaminosulfonyl, iso-butylaminosulfonyl, tert-butylaminosulfonyl.

15 Di-C1-C6-alkylaminosulfonyl is a radical of the formula RR'-N-S(0)2- wherein R and R' are independently of each other an alkyl radical having from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein. Examples include dimethylaminosulfonyl, diethylaminosulfonyl, N-methyl-N-ethylaminosulfonyl.

20 C6-C12 -Arylaminosulfonyl is a radical of the formula R-NH-S(0)2- wherein R is an aryl radical having from 6 to 12, preferably from 6 carbon atoms as defined herein.

Amino is NH2.

25 C1-C6 -Alkylamino is a radical of the formula R-NH- wherein R is an alkyl radical having from 1 to 6, in particular from 1 to 4 carbon atoms as defined herein. Examples include methylamino, ethylamino, n-propylamino, iso-propylamino, n-butylamino, 2-butylamino, iso-butylamino, tert-butylamino.

30 (Halogenated C1-C6 -alkyl)amino is a C1-C6 -alkylamino as defined herein, wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by 1, 2, 3, 4 or a corresponding number of identical or different halogen atoms.

Di-C1-C6-alkylamino is a radical of the formula RR'-N- wherein R and R' are independently of each other an alkyl radical having from 1 to 6, in particular from 1 to 4 carbon atoms as defined herein. Examples include dimethylamino, diethylamino, N-methyl-N-ethylamino.

Di-(halogenated C1-C6 -alkyl)amino is a di-C1-C6-alkylamino as defined herein, wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by 1, 2, 3, 4 or a corresponding number of identical or different halogen atoms.
Ci-C6-Alkylcarbonylamino is a radical of the formula R-C(0)-NH-, wherein R is an alkyl radical having from 1 to 6, in particular from 1 to 4 carbon atoms as defined herein. Examples include acetamido (methylcarbonylamino), propionamido, n-butyrnamido, 2-methylpropionamido (isopropylcarbonylamino), 2,2-dimethylpropionamido and the like.

(Halogenated Ci-C6-alkylcarbonylamino is a Ci-C6-alkylcarbonylamino as defined herein, wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by 1, 2, 3, 4 or a corresponding number of identical or different halogen atoms.

C6-C2-Arylcarbonylamino is a radical of the formula R-C(0)-NH-, wherein R is an aryl radical having from 6 to 12 carbon atoms as defined herein. Examples include phenylcarbonylamino.

C2-C6-Alkenylamino is a radical of the formula R-NH-, wherein R is a straight-chain or branched alkenyl group having from 2 to 6, in particular 2 to 4 carbon atoms. Examples include vinylamino, allylamino (2-propen-1-ylamino), 1-propen-1-ylamino, 2-propen-2-ylamino, methallylamino (2-methylprop-2-en-1-ylamino) and the like. C3-C7-Alkenylamino is, in particular, allylamino, 1-methylprop-2-en-1-ylamino, 2-buten-1-ylamino, 3-buten-1-ylamino, methallylamino, 2-penten-1-ylamino, 3-penten-1-ylamino, 4-penten-1-ylamino, 1-methylbut-2-en-1-ylamino or 2-ethylprop-2-en-1-ylamino.

Ci-C6-Alkylsulfonylamino is a radical of the formula R-S(0)2-NH-, wherein R is an alkyl radical having from 1 to 6, in particular from 1 to 4 carbon atoms as defined herein. Examples include methylsulfonylamino, ethylsulfonylamino, n-propylsulfonylamino, iso-propylsulfonylamino, n-butylsulfonylamino, 2-butylsulfonylamino, iso-butylsulfonylamino, tert-butylsulfonylamino.

(Halogenated C1-C6 alkyl)sulfonylamino is a Ci-C6-alkylsulfonylamino as defined herein, wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by 1, 2, 3, 4 or a corresponding number of identical or different halogen atoms.

C6-C2-Arylsulfonylamino is a radical of the formula R-S(0)2-NH-, wherein R is an aryl radical having from 6 to 12 carbon atoms as defined herein. Examples include phenylsulfonylamino.

Nitro is -NO2.

M1-M2-Heterocycl is a 3- to 12-membered heterocyclic radical including a saturated heterocyclic radical, which generally has 3, 4, 5, 6, or 7 ring forming atoms (ring members), an unsaturated non-aromatic heterocyclic radical, which generally has 5, 6 or 7 ring forming atoms, and a heteroaromatic radical (hetaryl), which generally has 5, 6 or 7 ring forming atoms. The heterocyclic radicals may be bound via a carbon atom (C-bound) or a nitrogen atom (N-bound). Preferred heterocyclic radicals comprise 1 nitrogen atom as ring member atom and optionally 1, 2 or 3 further heteroatoms as ring members, which are selected, independently of each other from O, S and N. Likewise
preferred heterocyclic radicals comprise 1 heteroatom as ring member, which is selected from O, S and N, and optionally 1, 2 or 3 further nitrogen atoms as ring members.

Examples of M₃-Mi₂-heterocycl include:

C- or N-bound 3-4-membered, saturated rings, such as
2-oxiranyl, 2-oxetanyl, 3-oxetanyl, 2-aziridinyl, 3-thietanyl, 1-azetidinyl, 2-azetidinyl, 3-azetidinyl;

C-bound, 5-membered, saturated rings, such as
tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydronethien-2-yl, tetrahydronethien-3-yl, tetrahydropyrrol-2-yl, tetrahydropyrrol-3-yl, tetrahydropyrazol-3-yl, tetrahydro-pyrazol-4-yl, tetrahydroisoxazol-3-yl, tetrahydroisoxazol-4-yl, tetrahydroisoxazol-5-yl, 1,2-oxathiolan-3-yl, 1,2-oxathiolan-4-yl, 1,2-oxathiolan-5-yl, tetrahydrothiofiao1-3-yl, tetrahydroisothiazol-4-yl, tetrahydroisothiazol-5-yl, 1,2-dithiolan-3-yl, 1,2-dithiolan-4-yl, tetrahydroimidazol-2-yl, tetrahydroimidazol-4-yl, tetrahydrothiazol-2-yl, tetrahydrothiazol-4-yl, tetrahydrothiazol-5-yl, 1,3-dioxolan-2-yl, 1,3-dioxolan-4-yl, 1,3-oxathiolan-2-yl, 1,3-oxathiolan-4-yl, 1,3-oxathiolan-5-yl, 1,3-dithiolan-2-yl, 1,3-dithiolan-4-yl, 1,3-dithiolan-5-yl,

C-bound, 6-membered, saturated rings, such as
tetrahydropyran-2-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, tetrahydrothiopyran-2-yl, tetrahydrothiopyran-3-yl, tetrahydrothiopyran-4-yl, 1,3-dioxan-2-yl, 1,3-dioxan-4-yl, 1,3-dioxan-5-yl, 1,4-dioxan-2-yl, 1,3-dithian-2-yl, 1,3-dithian-4-yl, 1,3-dithian-5-yl, 1,4-dithian-2-yl, 1,3-oxathiolan-2-yl, 1,3-oxathiolan-4-yl, 1,3-oxathiolan-5-yl, 1,3-oxathiolan-6-yl, 1,4-oxathian-2-yl, 1,4-oxathian-3-yl, 1,2-dithian-3-yl, 1,2-dithian-4-yl, hexahydro- pyrimidin-2-yl, hexahydro pyrimidin-4-yl, hexahydro pyrimidin-5-yl, hexahydro pyrazin-2-yl, hexahydro pyrazin-3-yl, hexahydro pyrazin-4-yl, hexahydro pyrazin-5-yl, hexahydro thiazol-2-yl, tetrahydro-1,3-oxazin-2-yl, tetrahydro-1,3-oxazin-4-yl, tetrahydro-1,3-oxazin-5-yl, tetrahydro-1,3-oxazin-6-yl, tetrahydro-1,3-thiazin-2-yl, tetrahydro-1,3-thiazin-4-yl, tetrahydro-1,3-thiazin-5-yl, tetrahydro-1,3-thiazin-6-yl, tetrahydro-1,4-thiazin-2-yl, tetrahydro-1,4-thiazin-3-yl, tetrahydro-1,4-thiazin-5-yl, tetrahydro-1,4-thiazin-6-yl,

N-bound, 5-membered, saturated rings, such as
tetrahydropyrrol-1-yl (pyrrolidin-1-yl), tetrahydropyrazol-1-yl, tetrahydro isoxazol-2-yl, tetrahydro isothiazol-2-yl, tetrahydroimidazol-1-yl, tetrahydrothiazol-3-yl;

N-bound, 6-membered, saturated rings, such as
piperidin-1-yl, hexahydro pyrimidin-1-yl, hexahydro pyrazin-1-yl, pyrrolidin-1-yl, hexahydro pyrazin-1-yl, tetrahydro-1,3-oxazin-3-yl, tetrahydro-1,3-thiazin-3-yl, tetrahydro-1,4-thiazin-4-yl, tetrahydro-1,4-oxazin-4-yl, morpholin-1-yl, tetrahydro-1,2-oxazin-2-yl;
C-bound, 5-membered, partially unsaturated rings, such as
2,3-dihydrofuran-2-yl, 2,3-dihydrofuran-3-yl, 2,5-dihydrofuran-2-yl, 2,5-dihydrofuran-3-yl, 4,5-dihydrofuran-2-yl, 2,3-dihydrofuran-2-yl, 2,3-dihydrofuran-3-yl, 2,3-dihydrothien-2-yl, 2,3-dihydrothien-3-yl, 2,5-dihydrothien-2-yl, 2,5-dihydrothien-3-yl, 4,5-dihydrothien-3-yl, 2,3-dihydro-1H-pyrrl-2-yl, 2,3-dihydro-1H-pyrrol-3-yl, 2,5-dihydro-1H-pyrrol-2-yl, 2,5-dihydro-1H-pyrrol-3-yl, 4,5-dihydro-1H-pyrrol-2-yl, 4,5-dihydro-1H-pyrrol-3-yl, 2,4-dihydro-2H-pyrrl-2-yl, 3,4-dihydro-2H-pyrrol-3-yl, 3,4-dihydro-5H-pyrrl-2-yl, 3,4-dihydro-5H-pyrrol-3-yl, 4,5-dihydro-1H-pyrazol-3-yl, 4,5-dihydro-1H-pyrazol-4-yl, 4,5-dihydro-1H-pyrazol-5-yl, 2,5-dihydro-1H-pyrrol-3-yl, 2,5-dihydro-1H-pyrrol-4-yl, 2,5-dihydro-1H-pyrrol-5-yl, 4,5-dihydrooxazol-3-yl, 4,5-dihydrooxazol-4-yl, 4,5-dihydrooxazol-5-yl, 2,5-dihydrooxazol-2-yl, 2,5-dihydrooxazol-3-yl, 2,5-dihydrooxazol-4-yl, 2,5-dihydrooxazol-5-yl, 2,3-dihydrooxazol-2-yl, 2,3-dihydrooxazol-3-yl, 2,3-dihydrooxazol-4-yl, 2,3-dihydrooxazol-5-yl, 4,5-dihydroisoxazol-3-yl, 4,5-dihydroisoxazol-4-yl, 4,5-dihydroisoxazol-5-yl, 2,5-dihydroisoxazol-3-yl, 2,5-dihydroisoxazol-4-yl, 2,5-dihydroisoxazol-5-yl, 2,3-dihydroisoxazol-3-yl, 2,3-dihydroisoxazol-4-yl, 2,3-dihydroisoxazol-5-yl, 4,5-dihydroisothiazol-3-yl, 4,5-dihydroisothiazol-4-yl, 4,5-dihydroisothiazol-5-yl, 2,5-dihydroisothiazol-3-yl, 2,5-dihydroisothiazol-4-yl, 2,5-dihydroisothiazol-5-yl, 2,3-dihydroisothiazol-3-yl, 2,3-dihydroisothiazol-4-yl, 2,3-dihydroisothiazol-5-yl, 4,5-dihydroimidazol-2-yl, 4,5-dihydroimidazol-3-yl, 4,5-dihydroimidazol-4-yl, 4,5-dihydroimidazol-5-yl, 2,5-dihydroimidazol-2-yl, 2,5-dihydroimidazol-3-yl, 2,5-dihydroimidazol-4-yl, 2,5-dihydroimidazol-5-yl, 1,3-dioxol-2-yl, 1,3-dioxol-4-yl, 1,3-dithiol-2-yl, 1,3-dithiol-4-yl, 1,3-oxathiol-2-yl, 1,3-oxathiol-4-yl, 1,3-oxathiol-5-yl;
N-bound, 5-membered, partially unsaturated rings, such as 2,3-dihydropyridazin-4-yl, 2,3-dihydropyridazin-5-yl, 2,3-dihydropyridazin-6-yl, 2H,6-dihydro-1,2-oxazin-4-yl, 2H,6-dihydro-1,2-thiazin-4-yl, 2H,6-dihydro-1,2-thiazin-5-yl, 2H,6-dihydro-1,2-thiazin-6-yl, 4H,5,6-dihydro-1,2-oxazin-4-yl, 4H,5,6-dihydro-1,2-oxazin-5-yl, 4H,5,6-dihydro-1,2-oxazin-6-yl, 4H,5,6-dihydro-1,2-thiazin-4-yl, 4H,5,6-dihydro-1,2-thiazin-5-yl, 4H,5,6-dihydro-1,2-thiazin-6-yl, 2H,3,6-dihydro-1,2-oxazin-4-yl, 2H,3,6-dihydro-1,2-oxazin-5-yl, 2H,3,6-dihydro-1,2-oxazin-6-yl, 2H,3,6-dihydro-1,2-thiazin-4-yl, 2H,3,6-dihydro-1,2-thiazin-5-yl, 2H,3,6-dihydro-1,2-thiazin-6-yl, 2H,3,4-dihydro-1,2-oxazin-4-yl, 2H,3,4-dihydro-1,2-oxazin-5-yl, 2H,3,4-dihydro-1,2-oxazin-6-yl, 2H,3,4-dihydro-1,2-thiazin-4-yl, 2H,3,4-dihydro-1,2-thiazin-5-yl, 2H,3,4-dihydro-1,2-thiazin-6-yl, 2,3,4,5-tetrahydropyridazin-3-yl, 2,3,4,5-tetrahydropyridazin-4-yl, 2,3,4,5-tetrahydropyridazin-5-yl, 2,3,4,5-tetrahydropyridazin-6-yl, 3,4,5,6-tetrahydropyridazin-3-yl, 3,4,5,6-tetrahydropyridazin-4-yl, 1,2,5,6-tetrahydropyridazin-3-yl, 1,2,5,6-tetrahydropyridazin-4-yl, 1,2,5,6-tetrahydropyridazin-5-yl, 1,2,5,6-tetrahydropyridazin-6-yl, 4H,5,6-dihydro-1,3-oxazin-2-yl, 4H,5,6-dihydro-1,3-oxazin-4-yl, 4H,5,6-dihydro-1,3-thiazin-2-yl, 4H,5,6-dihydro-1,3-thiazin-4-yl, 4H,5,6-dihydro-1,3-thiazin-5-yl, 4H,5,6-dihydro-1,3-thiazin-6-yl, 3,4,5,6-tetrahydropyrimidin-2-yl, 3,4,5,6-tetrahydropyrimidin-4-yl, 3,4,5,6-tetrahydropyrimidin-5-yl, 3,4,5,6-tetrahydropyrimidin-6-yl, 1,2,3,4-tetrahydropryanizin-2-yl, 1,2,3,4-tetrahydropryanizin-5-yl, 1,2,3,4-tetrahydropryanizin-6-yl, 1,2,3,4-tetrahydropryanizin-7-yl, 2,3-dihydro-1,4-thiazin-2-yl, 2,3-dihydro-1,4-thiazin-3-yl, 2,3-dihydro-1,4-thiazin-5-yl, 2,3-dihydro-1,4-thiazin-6-yl, 2H,1,3-oxazin-2-yl, 2H,1,3-oxazin-4-yl, 2H,1,3-oxazin-5-yl, 2H,1,3-oxazin-6-yl, 2H,1,3-thiazin-2-yl, 2H,1,3-thiazin-4-yl, 2H,1,3-thiazin-5-yl, 2H,1,3-thiazin-6-yl, 4H,1,3-oxazin-2-yl, 4H,1,3-oxazin-4-yl, 4H,1,3-oxazin-5-yl, 4H,1,3-oxazin-6-yl, 4H,1,3-thiazin-2-yl, 4H,1,3-thiazin-4-yl, 4H,1,3-thiazin-5-yl, 4H,1,3-thiazin-6-yl, 6H,1,3-oxazin-2-yl, 6H,1,3-oxazin-4-yl, 6H,1,3-oxazin-5-yl, 6H,1,3-oxazin-6-yl, 6H,1,3-thiazin-2-yl, 6H,1,3-thiazin-4-yl, 6H,1,3-thiazin-5-yl, 6H,1,3-thiazin-6-yl, 2H,1,4-oxazin-2-yl, 2H,1,4-oxazin-3-yl, 2H,1,4-oxazin-5-yl, 2H,1,4-oxazin-6-yl, 2H,1,4-thiazin-2-yl, 2H,1,4-thiazin-3-yl, 2H,1,4-thiazin-5-yl, 2H,1,4-thiazin-6-yl, 4H,1,4-oxazin-2-yl, 4H,1,4-oxazin-3-yl, 4H,1,4-oxazin-5-yl, 4H,1,4-thiazin-2-yl, 4H,1,4-thiazin-3-yl, 4H,1,4-thiazin-5-yl, 1,4-dihydropyridazin-3-yl, 1,4-dihydropyridazin-4-yl, 1,4-dihydropyridazin-5-yl, 1,4-dihydropyridazin-6-yl, 1,4-dihydropyridin-2-yl, 1,2-dihydropyrazin-2-yl, 1,2-dihydropyrazin-3-yl, 1,2-dihydropyrazin-5-yl, 1,2-dihydropyrazin-6-yl, 1,4-dihydropyrimidin-2-yl, 1,4-dihydropyrimidin-3-yl, 1,4-dihydropyrimidin-5-yl, 1,4-dihydropyrimidin-6-yl, 3,4-dihydropyrimidin-2-yl, 3,4-dihydropyrimidin-4-yl, 3,4-dihydropyrimidin-5-yl or 3,4-dihydropyrimidin-6-yl;
2,3-dihydro-1H-pyrrol-1-yl, 2,5-dihydro-1H-pyrrol-1-yl, 4,5-dihydro-1H-pyrazol-1-yl, 2,5-
dihydro-1H-pyrazol-1-yl, 2,3-dihydro-1H-pyrazol-1-yl, 2,5-dihydroisoxazol-2-yl, 2,3-
dihydroisoxazol-2-yl, 2,5-dihydroisothiazol-2-yl, 2,3-dihydroisoxazol-2-yl, 4,5-dihydro-1H-
imidazol-1-yl, 2,5-dihydro-1H-imidazol-1-yl, 2,3-dihydrooxazol-3-yl, 2,3-dihydrothiazol-3-yl;

N-bound, 6-membered, partially unsaturated rings, such as
1,2,3,4-tetrahydropyridin-1-yl, 1,2,5,6-tetrahydropyridin-1-yl, 1,4-dihydro-pyridin-1-yl, 1,2-
dihydropyridin-1-yl, 2H-5,6-dihydro-1,2-oxazin-2-yl, 2H-5,6-dihydro-1,2-thiazin-2-yl, 2H-3,6-
dihydro-1,2-oxazin-2-yl, 2H-3,6-dihydro-1,2-thiazin-2-yl, 2H-3,4-dihydro-1,2-oxazin-2-yl, 2H-3,4-
dihydro-1,2-thiazin-2-yl, 2,3,4,5-tetrahydropyridazin-2-yl, 1,2,5,6-tetrahydropyridazin-1-yl,
1,2,5,6-tetrahydropyridazin-2-yl, 1,2,3,6-tetrahydropyridazin-1-yl, 3,4,5,6-tetrahydroprymidin-3-
yl, 1,2,3,4-tetrahydropryanin-1-yl, 1,2,3,4-tetrahydroprymidin-1-yl, 1,2,3,4-tetrahydroprymidin-3-
yl, 2,3-dihydro-1,4-thiazin-4-yl, 2H-1,2-thiazin-2-yl, 4H-1,4-oxazin-4-yl, 4H-
1,4-thiazin-4-yl, 1,4-dihydropyrazin-1-yl, 1,2-dihydropyrazin-1-yl, 1,4-
dihydropyrimidin-1-yl or 3,4-dihydropyrimidin-3-yl;

C-bound, 5-membered, heteroaromatic rings, such as
2-furyl, 3-furyl, 2-thienyl, 3-thienyl, pyrrol-2-yl, pyrrol-3-yl, pyrazol-3-yl, pyrazol-4-yl, isoxazol-3-
yl, isoxazol-4-yl, isoxazol-5-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, imidazol-2-yl, im-
idazol-4-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, 1,2,3-
oxadiazol-4-yl, 1,2,3-oxadiazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-oxadia-
2-yl, 1,2,3-thiadiazol-4-yl, 1,2,3-thiadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 1,3,4-
thiadiazolyl-2-yl, 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl, tetrazol-5-yl;

C-bound, 6-membered, heteroaromatic rings, such as
pyridin-2-yl, pyridin-3-yl, pyridin-4-yl (4-pyridyl), pyridazin-3-yl, pyridazin-4-yl, pyrimidin-2-yl,
pyrimidin-4-yl, pyrimidin-5-yl, pyrazin-2-yl, 1,3,5-triazin-2-yl, 1,2,4-triazin-3-yl, 1,2,4-triazin-5-
yl, 1,2,4-triazin-6-yl, 1,2,4,5-tetrazin-3-yl;

N-bound, 5-membered, heteroaromatic rings, such as
pyrrol-1-yl, pyrazol-1-yl, imidazol-1-yl, 1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, tetrazol-1-yl.

Heterocyclyl also includes bicyclic heterocycles, which comprise one of the described 5- or 6-
membered heterocyclic rings and a further anellated, saturated or unsaturated or aromatic carbocyc-
ucle, such as a benzene, cyclohexane, cyclohexene or cyclohexadiene ring, or a further anellated 5- or
6-membered heterocyclic ring, this heterocyclic ring being saturated or unsaturated or aromatic.
These include quinolinyl, isoquinolinyl, indolyl, indoliziny, isodinolyl, indazolyl, benzofuryl,
benzthienyl, benzo[b]thiazolyl, benzoxazolyl, benzodioxide, benzthiazolyl and benzimidazolyl.
Examples of 5- or 6-membered heteroaromatic compounds comprising an anellated cycloalkeny1 ring
include dihydroindolyl, dihydroindoliziny, dihydroisoindolyl, dihydroquinolinyl, dihydroisoquino-
linyl, chromenyl and chromanyl.
M$_3$-M$_2$-Heteroarylene is a heteroaryl diradical. Examples include pyrid-2,5-ylene and pyrid-2,4-ylene.

With respect to the compounds’ capability of inhibiting glycine transporter 1, the variables $R^1$, $W$, $A^1$, $Q$, $Y$, $R^6$, $n_1$, $n_2$, $X^1$, $A$, $R^2$, $A^2$, $R^3$, $Y^1$, $R^{4a}$, $X^2$, $X^3$, $R^3$ have in particular the following meanings which, when taken alone or in combination, represent particular embodiments of the compounds of the formula (I) or any other formula disclosed herein.

In said formula (I), there may be one or more than one substituent $R^2$, $R^3$, $R^6$ and one or more than one substituent

More particularly, there may be up to 3 substituents $R^2$, up to 4 substituents $R^3$, and up to 6 substituents $R^6$. Preferably, there is one substituent

and 1, 2 or 3 substituents $R^2$. Formula (I) may thus be depicted as follows:

wherein $A$, $R^1$, $W$, $A^1$, $Q$, $Y$, $R^6$, $n_2$, $X^1$, $R^2$, $A^2$, $R^3$, $Y^1$, $R^{4a}$, $X^2$, $X^3$ and $R^3$ are as defined herein, $a$ is 1, 2 or 3, $b$ is 1, 2, 3 or 4, $c$ is 1 and $d$ is 1, 2, 3, 4, 5 or 6. If there is more than one radical $R^2$, these may be the same or different radicals. If there is more than one radical $R^3$, these may be the same or different radicals. If there is more than one radical $R^6$, these may be the same or different radicals. According to one embodiment, $a$ is 1, $b$ is 1 or 2, $c$ is 1, and $d$ is 1 or 2.
In the following the radical

\[
\begin{array}{c}
R^1 \quad W \quad A^1 \quad Q \quad Y \\
\end{array}
\]

is also referred to as R.

A is a 5- or 6-membered ring which includes two carbon atoms from the tetrahydropyran, tetrahydrothiopyran and tetrahydropyridine moiety to which A is fused. A may be a homocyclic or heterocyclic ring. The ring may be saturated, unsaturated non-aromatic or aromatic. According to a particular embodiment, A is a benzene ring. As a heterocyclic ring, A may include 1, 2 or 3 heteroatoms as ring member atoms, which are selected, independently of each other from N, S and O. Preferred heterocyclic rings comprise 1 nitrogen atom as ring member atom and optionally 1 or 2 further heteroatoms as ring members, which are selected, independently of each other from O, S and N. Likewise preferred heterocyclic rings comprise 1 heteroatom as ring member atom, which is selected from O, S and N, and optionally 1 or 2 further nitrogen atoms as ring member atoms. According to a particular embodiment, A is a heterocyclic ring selected from the group consisting of the following 5- or 6-membered heterocyclic rings:
In said formulae, hydrogen atoms are not depicted. This is meant to illustrate that the free valency of a carbon or nitrogen atom may be either bound to a hydrogen atom, to R or to R². Accordingly, R and R² may be C- or N-bound at any position of ring A.

The skilled person will appreciate that some of the rings depicted above may be represented with a different structure, e.g. with hydrogen atoms having other positions than those shown above, for instance as given in the following structures:

Preferably, A is a heterocyclic ring selected from the group consisting of the following 5- or 6-membered heterocyclic rings:
If ring A is a 5-membered heterocyclic ring it is preferred that R is bound to $G^1$ or $G^2$, in particular $G^2$:

![Diagram]

In said formula, $G^1$, $G^2$ and $G^3$ independently are -CH=, -CH$_2$, -N=, -NH-, S or O, at least one of $G^1$, $G^2$ and $G^3$ is -CH= or -CH$_2$, the dotted line represents a single or a double bond and $A^2$, $R^3$, $Y^1$, $R^{4a}$, $R^{4b}$, $X^2$, $X^3$, $R^5$ are as defined herein.

If ring A is 6-membered heterocyclic ring it is preferred that R is bound to $G^1$ or $G^2$, in particular $G^2$:

![Diagram]

In said formula, $G^1$, $G^2$, $G^3$ and $G^4$ independently are -CH=, -CH$_2$, -N=, -NH-, S or O, at least one of $G^1$, $G^2$, $G^3$ and $G^4$ is -CH= or -CH$_2$, the dotted line represents a single or a double bond and $A^2$, $R^3$, $Y^1$, $R^{4a}$, $R^{4b}$, $X^2$, $X^3$, $R^5$ are as defined herein.
Heterocyclic compounds having the following partial structures are preferred:

Heterocyclic compounds having the following partial structures are particularly preferred:
In said formulae, R and R² are as defined herein. If there is more than one radical R², these may be the same or different radicals.

5

R¹ is hydrogen, Ci-C₆-alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl or n-pentyl),
c₃-c₁₂-cycloalkyl-Ci-C₄-alkyl (e.g. cyclopropylmethyl, cyclopentylmethyl or cyclohexylmethyl),
halogenated Ci-C₆-alkyl (e.g. 3-fluoroprop-1 -yl, 3-chloroprop-1 -yl or 3,3,3-trifluoroprop-1 -yl), tri-(Ci-C₄-alkyl)-silyl-Ci-C₄-alkyl (e.g. trimethylsilyl), hydroxy-Ci-C₄-alkyl, Ci-C₆-alkoxy-Ci-C₄-
alkyl (e.g. ethoxyethyl), amino-Ci-C₄-alkyl, Ci-C₆-alkylaminocarbonyl-Ci-C₄-alkyl, di-Ci-C₆-
alkylamino-Ci-C₄-alkyl, Ci-C₆-alkylcarbonylamino-Ci-C₄-alkyl, Ci-C₆-alkoxy carbonylamino-Ci-
C₄-alkyl, Ci-C₆-alkylaminocarbonylamino-Ci-C₄-alkyl, di-Ci-C₆-alkylaminocarbonylamino-Ci-C₄-
alkyl, Ci-C₆-alkylsulfonylamino-Ci-C₄-alkyl, (optionally substituted c₆-c₁₂ -aryl-Ci-C₆-
alkylamino)-Ci-C₄-alkyl, optionally substituted c₆-c₁₂ -aryl-Ci-C₄-alkyl, optionally substituted M₃-
C₆₂-heterocyclyl-Ci-C₄-alkyl, C₃-C₂-cycloalkyl (e.g. cyclopropyl or cyclobutyl), Ci-C₆-
alkylcarbonyl, Ci-C₆-alkoxy carbonyl, halogenated Ci-C₆-alkoxy carbonyl, c₆-c₁₂ -aryloxycarbonyl,
aminocarbonyl, Ci-C₆-alkylaminocarbonyl, (halogenated Ci-C₄-alkyl)aminocarbonyl, C₆-C₁₂-
arylaminocarbonyl, C₂-C₆-alkenyl (e.g. prop-1,2-en-1 -yl), C₂-C₆-alkenyl, optionally substituted C₆-
Ci₂-aryl (e.g. phenyl, 2-methylphenyl), hydroxy, Ci-C₆-alkoxy (e.g. tert-butyl), halogenated C₆-
C₆₂-alkoxy, Ci-C₆-hydroxyalkoxy, Ci-C₆-alkoxy-Ci-C₄-alkoxy, amino-Ci-C₆-alkoxy, Ci-C₆-
alkylamino-Ci-C₄-alkoxy, di-Ci-C₆-alkylaminocarbonyl-Ci-C₄-alkoxy, Ci-C₆-alkylcarbonylamino-Ci-
C₄-alkoxy, c₆-c₁₂ -arylcarbonylamino-Ci-C₄-alkoxy, Ci-C₆-alkoxy carbonylamino-Ci-C₄-alkoxy, Ci-
C₂-aryl-Ci-C₄-alkoxy, Ci-C₆-alkylsulfonylamino-Ci-C₄-alkoxy, (halogenated C₆-C₁₂-
alkyl)sulfonylamino-Ci-C₄-alkoxy, c₆-c₁₂ -arylsulfonylamino-Ci-C₄-alkoxy, (c₆-c₁₂ -aryl-Ci-C₆-
alkyl)sulfonylamino-Ci-C₄-alkoxy, M₃-M₂-heterocyclylsulfonylamino-Ci-C₄-alkoxy, M₃-M₂-
heterocyclyl-Ci-C₄-alkoxy, c₆-c₁₂ -aryloxy, M₃-M₁₂-heterocyclyxoxy, Ci-C₆-alkylthio, halogenated
Ci-C₆-alkylthio, Ci-C₆-alkylamino, (halogenated Ci-C₆-alkyl) amino, di-Ci-C₆-alkylamino (e.g.
dimethylamino), di-(halogenated Ci-C₆-alkyl)amino, Ci-C₆-alkylcarbonylamino, (halogenated C₆-
c₆₂-alkyl)carbonylamino, c₆-c₁₂ -arylcarbonylamino, Ci-C₆-alkylationamino, (halogenated C₆-
c₆₂-alkyl)sulfonylamino, c₆-c₁₂ -arylsulfonylamino or optionally substituted M₂-M₁₂-heterocyclyl
(e.g. 3-pyridyl, 2-pyridyl, 2-thienyl, 4-methyl-2-thienyl, 5-methyl-2-thienyl, 5-chloro-2-thienyl,
2,5-dimethyl-3-thienyl, 1,2-diazol-4-yl, 1-methyl-1,2-diazol-4-yl, 1,3-dimethyl-1,2-diazol-4-yl, 1,
1-ethyl-1,2-diazol-4-yl, 1-difluormethyl-1,2-diazol-4-yl, 2-methyl-1,3-diazol-4-yl, 1-methyl-1,3-
diazol-4-yl, 2-methyl-1,3-thiazol-5-yl, 2,4-dimethyl-1,3-thiazol-5-yl, 3-pyrrolidinyl, 1-methyl-
pyrrol-3-yl, 2-pyridyl, 1-methyl-1,2-diazol-3-yl, 1-methyl-3-trifluoromethyl-1,2-diazol-4-yl, 1,2-
dimethyl-1,3-diazol-4-yl, 5-methylisoxazol-3-yl, 1-methyl-1,2,4-triazol-1-3-yl, 1-methyl-1,2,3-
diazol-4-yl, 1-ethyl-1,2,3-thiazol-4-yl, furan-3-yl, 5-methyl-furan-2-yl, 2,5-dimethyl-furan-3-yl, 3-
methyl-piperidinyl, thiophen-2-yl, 4-methyl-thiophen-2-yl, 5-methyl-thiophen-2-yl, thiophen-3-yl, or morpholin-4-yl).

Preferably, R¹ is C₆-C₆-alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, sec-butyl, n-butyl or n-pentyl), c₃-C₅-cycloalkyl-C₆-C₄-alkyl (e.g. cyclopropylmethyl, cyclopentylmethyl or cyclohexylmethyl), halogenated C₆-C₆-alkyl (e.g. 3-fluoroprop-l-yl, 3-chloroprop-l-yl or 3,3,3-trifluoroprop-l-yl), tri-(C₄-C₆-alkyl)-silyl-C₄₆-alkyl (e.g. trimethylsilylalkyl), C₆-C₆-alkyloxycarbonyl (e.g. ethoxycarbonyl), amino-C₆-C₆-alkyl, C₆-C₆-alkylamino-C₄-C₄-alkyl, di-C₆-C₆-alkylamino-C₄-C₄-alkyl, C₆-C₆-alkylamino-C₆-C₆-alkylamino, C₆-C₆-alkylamino-C₆-C₆-alkylamino, (halogenated C₆-C₆-alkylamino, di-C₆-C₆-alkylamino or optionally substituted M₃-M₄-heterocyclyl (e.g. 3-pyridyl, 2-pyridyl, 2-thienyl, 4-methyl-2-thienyl, 5-methyl-2-thienyl, 5-chloro-2-thienyl, 2,5-dimethyl-3-thienyl, 1,2-diazol-4-yl, 1-methyl-1,2-diazol-4-yl, 1,3-dimethyl-1,2-diazol-4-yl, 1-ethyl-1,2-diazol-4-yl, 1-difluormethyl-1,2-diazol-4-yl, 2-methyl-1,3-diazol-4-yl, 1-methyl-1,3-diazol-4-yl, 2-methyl-1,3-thiazol-5-yl, 2,4-dimethyl-1,3-thiazol-5-yl, 1-methyl-1,2,3-triazol-4-yl, 1-ethyl-1,2,3-triazol-4-yl, 3-pyrollidinyl, furan-3-yl, 5-methyl-furan-2-yl, 2,5-dimethyl-furan-3-yl, 3-methyl-piperidinyl, thiophen-2-yl, 4-methyl-thiophen-2-yl, 5-methyl-thiophen-2-yl, thiophen-3-yl, or morpholin-4-yl).

More preferably, R¹ is C₆-C₆-alkyl (e.g. ethyl, n-propyl, isopropyl, 2-butyl), c₃-C₅-cycloalkyl-d-c₄-alkyl (e.g. cyclopropylmethyl), c₃-C₅-cycloalkyl (e.g. cyclobutyl), or optionally substituted M₃-M₄-heterocyclyl (e.g. 3-pyridyl, 2-pyridyl, 1-methyl-1,2-diazol-4-yl, 1,3-dimethyl-1,2-diazol-4-yl, 1-ethyl-1,2-diazol-4-yl, 1-methyl-1,3-diazol-4-yl, 1-ethyl-1,2,3-triazol-4-yl, 1-ethyl-1,2,3-triazol-4-yl, 3-oxetanyl, 1-methyl-pyrrol-3-yl, furan-3-yl, 5-methyl-furan-2-yl, 2,5-dimethyl-furan-3-yl, 3-methyl-piperidinyl, thiophen-2-yl, 4-methyl-thiophen-2-yl, 5-methyl-thiophen-2-yl, thiophen-3-yl, or morpholin-4-yl).

According to a particular embodiment, R¹ is C₆-C₆-alkyl (e.g. ethyl, n-propyl, isopropyl, 2-butyl), c₃-C₅-cycloalkyl-C₆-C₄-alkyl (e.g. cyclopropylmethyl), or c₃-C₅-cycloalkyl (e.g. cyclobutyl).

In connection with R¹, substituted C₆-C₆-aryl in particular includes C₆-C₆-aryl, such as phenyl or naphthyl, substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, C₆-C₆-alkyl, C₆-C₄-haloalkyl, cyano, C₆-C₆-alkoxy, amino, C₆-C₆-alkylamino, C₆-C₆-dialkylamino, morpholinyl and piperidinyl. The same applies to substituted C₆-C₆-aryl-C₄-alkyl.

In connection with R¹, substituted M₃-M₄-heterocyclyl in particular includes M₃-M₄-heterocyclyl, such as pyridyl, thienyl, diazolyl, quinolinyl, furanyl, thiophenyl, piperidinyl, pyrazinyl or morpholinyl, pyrrolyl, isoxazolyl and triazolyl being further examples of such M₃-M₄-heterocyclyl, substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, C₆-C₆-alkyl, C₆-C₆-alkoxy, amino, C₆-C₆-alkylamino, C₂₆-C₆.
alkylsulfonyl, amino, C1-C4 -alkylamino, C1-C4 -dialkylamino, C6-C12 -arylamino and M3-M12- heterocyclyl (e.g., morpholinyl or piperidinyl). The same applies to substituted M3-M12- heterocyclyl in substituted M3-M12-heterocyclyl-C1-C4-alkyl.

W is -NR7- or a bond. Y is -NR8- or a bond. According to one embodiment, W is -NR2- and Y is a bond. According to an alternative embodiment, W is a bond and Y is -NR8-. According to a further alternative embodiment, W is a bond and Y is a bond, especially if R1 is a nitrogen-bound radical, e.g. nitrogen-bound heterocyclyl such as piperazinyl or morpholinyl.

Q is -S(0)2- or -C(O)-. According to one embodiment, Q is -S(0)2-, especially if Y is -NR8-. According to a preferred embodiment, -Q-Y- is -S(0)2-NR8-.

According to a particular embodiment, -W-A'Q-Y- is -W-A'S(0)2-NR8-, -NR7-S(0)2-, -A'S(0)2- or -S(0)2-. According to a further particular embodiment, -W-A'Q-Y- is -W-A'CO-NR8- or -NR7-CO-.

A1 is optionally substituted C1-C4 -alkylene or a bond. In connection with A1, substituted C1-C4-alkylene in particular includes C1-C4 -alkylene substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, C1-C4 -alkyl and cyano. Preferably, A1 is a bond. If A1 is C1-C4-alkylene, W is preferably NR7-.

According to a particular embodiment, R'-W-A'Q-Y- is R1S(0)2-NH-, R1NH5-S(0)2-, R'-CCO)-NH- or R'-NH-CCO)-.

According to a further particular embodiment, W is a bond and A1 is a bond.

The index n1 is 0, 1, 2, or 3. Preferably, n1 is 1, 2 or 3. In particular, n1 is 1 or 2.

The index n2 is 0, 1, 2, or 3. Preferably, n2 is 1, 2, or 3. In particular, n2 is 1 or 2.

According to a particular embodiment, at least one of n1 and n2 is 1, 2, or 3.
The following examples of cyclic moieties illustrate combinations of n₁ and n₂:

wherein X₁ and R⁶ are as defined herein.

According to a further particular embodiment, the sum of n₁ and n₂ is 2, 3, or 4.

According to a further particular embodiment, combinations of n₁ and n₂ include n₁=1, n₂=1; n₁=1, n₂=2; n₁=2, n₂=1; n₁=2, n₂=2; n₁=1, n₂=3; or n₁=3, n₂=1.

According to one embodiment, X₁ is >N-. According to an alternative embodiment, X₁ is >CH-.

The following examples of cyclic moieties illustrate preferred combinations of n₁, n₂ and X₁:
wherein R\textsubscript{6} is as defined herein.

More preferred combinations of n\textsubscript{l}, n\textsubscript{2} and X\textsubscript{1} include cyclic moieties where

n\textsubscript{l} is 1, n\textsubscript{2} is 1 and X\textsubscript{1} is ->N-; n\textsubscript{l} is 1, n\textsubscript{2} is 1 and X\textsubscript{1} is >CH-; n\textsubscript{l} is 1, n\textsubscript{2} is 2 and X\textsubscript{1} is ->N-; n\textsubscript{l} is 1, n\textsubscript{2} is 2 and X\textsubscript{1} is >CH-; n\textsubscript{l} is 2, n\textsubscript{2} is 1 and X\textsubscript{1} is ->N-; n\textsubscript{l} is 2, n\textsubscript{2} is 1 and X\textsubscript{1} is >CH-; n\textsubscript{l} is 2, n\textsubscript{2} is 2 and X\textsubscript{1} is ->N-; n\textsubscript{l} is 2, n\textsubscript{2} is 2 and X\textsubscript{1} is >CH-; n\textsubscript{l} is 3, n\textsubscript{2} is 1 and X\textsubscript{1} is ->N-; n\textsubscript{l} is 3, n\textsubscript{2} is 1 and X\textsubscript{1} is >CH-; or n\textsubscript{l} is 3, n\textsubscript{2} is 1 and X\textsubscript{1} is >CH-.

The cyclic moieties may thus be depicted by the following formulae:

wherein R\textsubscript{6} is as defined herein.
Particularly preferred combinations of n1, n2 and X1 include moieties where n1 is 1, n2 is 1 and X1 is ->N- (azetidinyl); or n1 is 1, n2 is 1 and X1 is >CH- (cyclobutyl).

The substituents R1-W-A'Q-Y- and -A on the cyclic moiety can be cis- or trans-configuration as depicted by the following formula:

![Diagram](attachment:image.png)

wherein R1, W, A1, Q, Y, R6, n1, n2, X1 and A are as defined herein.

According to a particular embodiment, the substituents R1-W-A'Q-Y- and -A are in trans-configuration.

In formula (I), there may be one or more than one radical R6. More particularly, there may be up to 6 radicals R6. Preferably, there may be up to 4 radical R6. In particular, there may be one or 2 radicals R6. If there is more than one radical R6, these may be the same or different radicals. The compounds of the invention may therefore be represented by the following formula:
wherein R, R*, Rd, R independently have one of the meanings given for R^6, and A, R^1, W, A^1, Q, Y, R^6, X^1, n1, n2, R^2, A^2, R^3, Y^1, R^4, R^4b, X^2, X^3, R^5 are as defined herein (with X^1 being >N- or >CR^6- and R^6 having one of the meanings given for R^6).

According to a particular embodiment, the compounds of the invention have the following formula:

wherein R^6 has one of the meanings given for R^6, and A, R^1, W, A^1, Q, Y, R^6, X^1, n1, n2, R^2, A^2, R^3, Y^1, R^4b, R^4b, X^2, X^3, R^5 are as defined herein.

R^6 is hydrogen, halogen (e.g. fluorine), C_1-C_4-alkyl (e.g. methyl or ethyl), halogenated C_1-C_4-alkyl (e.g. 1,1,1-trifluoromethyl-yl), -CN, hydroxy, C_6-alkoxy (e.g. methoxy), or halogenated C_6-alkoxy.

According to an alternative embodiment, two R^6 together with the carbon atom to which they are bound may form a carbonyl.

The following examples of cyclic moieties illustrate combinations of n1, n2 and R^6, wherein two R^6 together with the carbon atom to which they are bound form a carbonyl:
The following examples of cyclic moieties illustrate particular combinations of $n_1$, $n_2$ and $R^5$, wherein two $R^6$ together with the carbon atom to which they are bound form a carbonyl:

Preferably, $R^6$ is hydrogen or $C_1$-$C_4$-alkyl (e.g. methyl, ethyl). In particular, $R^6$ is hydrogen.
If A is a benzene ring, the radical

\[ \begin{align*}
R^1 & \quad W \quad A^1 \quad Q \quad Y \\
& \quad R^6 \quad n_1 \quad J \quad \cdots \quad m_0
\end{align*} \]

may, in principle, be bound to the 5-, 6-, 7- or 8-position of the skeleton of the compounds of the invention:
In said formulae, $R^1$, $W$, $A^1$, $Q$, $Y$, $R^6$, $X^1$, $n_1$, $n_2$, $R^2$, $A^2$, $R^3$, $Y^1$, $R^{4a}$, $R^{4b}$, $X^2$, $X^3$, $R^5$ are as defined herein.

Compounds of the invention having the radical
in the 5-, 6-, 7-position are preferred.

Particularly preferred are compounds of the invention having the radical

\[
\begin{array}{c}
R^1 \quad W \quad A^1 \quad Q \quad Y \\
\end{array}
\]

5

in the 6-position.

In addition to the radical

\[
\begin{array}{c}
R^1 \quad W \quad A^1 \quad Q \quad Y \\
\end{array}
\]

the compounds of the invention may have one or more than one further substituent bound to the ring A. In these positions, the skeleton of the compounds of the invention may thus be substituted with one or more than one radical R^2. If there is more than one radical R^2, these may be the same or different radicals. In particular, the skeleton of the compounds of the invention may be substituted with one or more than one radical R^2 in 5-, 6-, 7- and/or 8-position if A is a benzene ring. The compounds of the invention may therefore be represented by one of the following formulae:
wherein $R_2^a$, $R_2^b$, $R_2^c$, $R_2^d$ independently have one of the meanings given for $R_2$, and $R_1^l$, $W$, $A_1^l$, $Q$, $Y$, $R_6^l$, $X_1^l$, $n_l$, $n_2$, $R_2^l$, $A_2^l$, $R_3^l$, $Y_1^l$, $R_4^l$, $R_{4b}$, $X_2^l$, $X_3^l$, $R_5^l$ are as defined herein.
R² is hydrogen, halogen (e.g. fluorine), Ci-C6-alkyl, halogenated C₁-C₄-alkyl, -CN, C₂-C₆-alkenyl, C₂-C₆-alkynyl, optionally substituted C₆-Ci₂-aryl, hydroxy, Ci-C6-alkoxy, halogenated Ci-Ce-alkoxy, Ci-C6-alkoxy carbonyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, optionally substituted C₆-Ci₂-aryl-Ci-C₄-alkoxy, Ci-Ce-alkylcarbonyloxy, Ci-C₆-alkylthio, Ci-C₆-alkylsulfinyl, Ci-C₆-alkylsulfonyl, aminosulfonyl, amino, Ci-C₆-alkylamino, C₂-C₆-alkenylamino, nitro or optionally substituted M₃-M₁₂-heterocyclyl, or two radicals R² together with the ring atoms of A to which they are bound form a 5- or 6-membered ring.

An optionally substituted 5- or 6-membered ring that is formed by two radicals R² together with the ring atoms of A to which they are bound is, for instance, a benzene ring.

In connection with R², substituted C₆-Ci₂-aryl in particular includes C₆-Ci₂-aryl, such as phenyl, substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, Ci-C₄-alkyl, Ci-C₄-haloalkyl, cyano, Ci-C₄-alkoxy and Ci-C₄-haloalkoxy.

In connection with R², substituted M₃-M₁₂-heterocyclyl in particular includes M₃-M₁₂-heterocyclyl, such as morpholinyl, pyrrolidinyl and piperidinyl, substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, Ci-C₄-alkyl, Ci-C₄-haloalkyl, cyano, Ci-C₄-alkoxy and C₁-C₄-haloalkoxy.

Preferably, R² is hydrogen, halogen (e.g. fluorine), CN or Ci-C₆-alkoxy. In particular, R² is hydrogen or halogen (e.g. fluorine).

According to a particular embodiment, the compounds of the invention have one of the following formulae:
In 2-, 3- and/or 4-position, the compounds of the invention may be substituted with one or more than one radical $R$. If there is more than one radical $R$, these may be the same or different radicals. The compounds of the invention may therefore be represented by the following formula:

In 2-, 3- and/or 4-position, the compounds of the invention may be substituted with one or more than one radical $R$. If there is more than one radical $R$, these may be the same or different radicals. The compounds of the invention may therefore be represented by the following formula:

$A^2$ is $-O-$, $-S-$ or $-NR^6$. According to a preferred embodiment, $A^2$ is $-O-$. 

In 2-, 3- and/or 4-position, the compounds of the invention may be substituted with one or more than one radical $R$. If there is more than one radical $R$, these may be the same or different radicals. The compounds of the invention may therefore be represented by the following formula:
wherein $R_1$, $R_2$, $R_3$, $R_4$, $d$ independently have one of the meanings given for $R_3$, and $A$, $R_1$, $W$, $A_1$, $Q$, $Y$, $R_6$, $n_1$, $n_2$, $X_1$, $R_2$, $A_2$, $R_3$, $Y_1$, $R_4$, $R_4$, $X_2$, $X_3$, $R_5$ are as defined herein.

According to a particular embodiment, the compounds of the invention have one of the following formulae:

wherein $R_1$, $R_2$, $R_3$, $R_5$ independently have the meaning of $R_3$ and $A$, $R_1$, $W$, $A_1$, $Q$, $Y$, $R_6$, $n_1$, $n_2$, $X_1$, $R_2$, $A_2$, $R_3$, $Y_1$, $R_4$, $R_4$, $X_2$, $X_3$, $R_5$ are as defined herein.
R³ is hydrogen, halogen, Ci-Ce-alkyl, Ci-C6-alkoxy, or two radicals R³ together with the carbon atom to which they are attached form a carbonyl group.

Preferably, R³ is hydrogen or Ci-C6-alkyl (e.g. methyl). In particular, R³ is hydrogen.

Y¹ is a bond or optionally substituted CpC₄-alkylene (e.g. methylene or 1,2-ethylene). In connection with Y¹, substituted Ci-C₆-alkylene in particular includes Ci-C₆-alkylene substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, CpC₄-alkyl, CpC₄-haloalkyl, C₃-Ci-C₂-cycloalkyl and cyano. In particular, Y¹ is a bond.

R⁴⁵ is hydrogen, CpC₆-alkyl (e.g. methyl, ethyl, n-propyl or isopropyl), C₃-Ci-C₂-cycloalkyl-CpC₄-alkyl (e.g. cyclopropylmethyl), halogenated CpC₄-alkyl (e.g. 2-fluoroethyl or 2,2,2-trifluoroethyl), hydroxy-Ci-C₄-alkyl, Ci-C₆-alkoxy-Ci-C₄-alkyl, amino-Ci-C₄-alkyl, -CH₂-CN, C₆-Cᵢ-C₂-aryl-Ci-C₄-alkyl (e.g. benzyl), optionally substituted C₃-Ci-C₂-cycloalkyl (e.g. cyclopropyl or cyclobutyl), -CHO, Ci-C₄-alkylcarbonyl (e.g. methylcarbonyl, ethylcarbonyl or isopropylcarbonyl), (halogenated CpC₄-alkyl)carbonyl (e.g. fluoromethylcarbonyl, difluoromethylcarbonyl, trifluoromethylcarbonyl, 1,1,1-trifluoroeth-2-ylcarbonyl or 1,1,1-trifluoroprop-3-ylcarbonyl), Cᵢ-C₆-arylcarbonyl (e.g. phenylcarbonyl), CpC₄-alkoxy carbonyl (e.g. ethoxycarbonyl or tert-butoxycarbonyl), C₆-Cᵢ₂-arlyloxy carbonyl (e.g. phenoxy carbonyl), CpC₆-alkylaminocarbonyl, C₆-Cᵢ₆-alkenyl, -C(=NH)NH₂, -C(=NH)HNHCN, CpC₆-alkylsulfonyl, C₆-Ci₂-arylsulfonyl, amino, -NO or optionally substituted M₃-Mi₂-heterocyclyl (e.g. 3-oxetanyl).

In connection with R⁴⁵, substituted C₃-Ci-C₂-cycloalkyl in particular includes C₃-Ci-C₂-cycloalkyl such as cyclopropyl, cyclobutyl or cyclohexyl, substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, optionally substituted CpC₆-alkyl, halogenated CpC₆-alkyl, CN, hydroxy, CpC₆-alkoxy, halogenated CpC₆-alkoxy, amino, CpC₆-alkylamino, di-CpC₆-alkylamino and M₃-Mi₂-heterocyclyl.

In connection with R⁴⁵, substituted M₃-Mi₂-heterocyclyl in particular includes M₃-Mi₂-heterocyclyl substituted with 1 or more substituents R⁴⁶ and/or R⁴⁷. The compounds of the invention may therefore be represented by the following formula:

![Diagram](https://example.com/diagram.png)

wherein A, R¹, W, A¹, Q, Y, R⁶, nl, n₂, X¹, R², A², R³, Y^R*, X², X³ and R⁵ are as defined herein.
\( \text{R}^{3*} \) is hydrogen, halogen, C\(_{6}\)-alkyl, C\(_{3}-C_{12} \)-cycloalkyl-C\(_{4}\)-alkyl, halogenated C\(_{6}\)-alkyl, tri-(C\(_{4}\)-alkyl)silyl-C\(_{4}\)-alkyl, hydroxy-C\(_{4}\)-alkyl, C\(_{6}\)-alkoxy-C\(_{4}\)-alkyl, amino-C\(_{4}\)-alkyl, C\(_{6}\)-alkylamino-C\(_{4}\)-alkyl, di-C\(_{6}\)-alkylamino-C\(_{4}\)-alkyl, C\(_{6}\)-alkylcarbonylamino-C\(_{4}\)-alkyl, C\(_{6}\)-alkylaminocarbonylamino-C\(_{4}\)-alkyl, di-C\(_{6}\)-alkylaminocarbonylamino-C\(_{4}\)-alkyl, C\(_{6}\)-alkylsulfonylamino-C\(_{4}\)-alkyl, (optionally substituted C\(_{6}-C_{12} \)-aryl-Ci-C\(_{4}\)-alkylamino-C\(_{4}\)-alkyl, optionally substituted C\(_{6}-C_{12} \)-heterocyclyl-Ci-C\(_{4}\)-alkyl, C\(_{6}-C_{12} \)-cycloalkyl, C\(_{6}-C_{12} \)-alkylcarbonyl, C\(_{6}\)-alkylaminocarbonyl, halogenated C\(_{6}\)-alkylaminocarbonyl, C\(_{6}-C_{12} \)-aryloxycarbonyl, aminocarbonyl, C\(_{6}\)-alkylaminocarbonyl, (halogenated C\(_{6}-C_{4}\)-alkyl)aminocarbonyl, C\(_{6}-C_{12} \)-aryloxycarbonyl, C\(_{6}-C_{12} \)-alkylaminocarbonyl, C\(_{6}-C_{12} \)-alkylaminocarbonyl or optionally substituted C\(_{6}-C_{12} \)-heterocyclyl,

\( \text{R}^{4*} \) is hydrogen, halogen, C\(_{6}\)-alkyl, C\(_{3}-C_{12} \)-cycloalkyl-Ci-C\(_{4}\)-alkyl, halogenated C\(_{6}\)-alkyl, tri-(C\(_{4}\)-alkyl)silyl-C\(_{4}\)-alkyl, hydroxy-C\(_{4}\)-alkyl, C\(_{6}\)-alkoxy-C\(_{4}\)-alkyl, amino-C\(_{4}\)-alkyl, C\(_{6}\)-alkylamino-C\(_{4}\)-alkyl, di-C\(_{6}\)-alkylamino-C\(_{4}\)-alkyl, C\(_{6}\)-alkylcarbonylamino-C\(_{4}\)-alkyl, C\(_{6}\)-alkylaminocarbonylamino-C\(_{4}\)-alkyl, di-C\(_{6}\)-alkylaminocarbonylamino-C\(_{4}\)-alkyl, C\(_{6}\)-alkylsulfonylamino-C\(_{4}\)-alkyl, (optionally substituted C\(_{6}-C_{12} \)-aryl-Ci-C\(_{4}\)-alkylamino-C\(_{4}\)-alkyl, optionally substituted C\(_{6}-C_{12} \)-heterocyclyl-Ci-C\(_{4}\)-alkyl, C\(_{6}-C_{12} \)-cycloalkyl, C\(_{6}-C_{12} \)-alkylcarbonyl, C\(_{6}\)-alkylaminocarbonyl, halogenated C\(_{6}\)-alkylaminocarbonyl, C\(_{6}-C_{12} \)-aryloxycarbonyl, aminocarbonyl, C\(_{6}\)-alkylaminocarbonyl, (halogenated C\(_{6}-C_{4}\)-alkyl)aminocarbonyl, C\(_{6}-C_{12} \)-aryloxycarbonyl, C\(_{6}-C_{12} \)-alkylaminocarbonyl, C\(_{6}-C_{12} \)-alkylaminocarbonyl or optionally substituted C\(_{6}-C_{12} \)-heterocyclyl,
C₆-alkyl)carbonylamino, C₆-C₁₂ -arylcarbonylamino, (halogenated C₁-
C₆-alkyl)sulfonylamino, C₆-C₁₂ -arylcarbonylamino or optionally substituted C₃-C₁₂ -heterocyclyl,

the index q is 1, 2 or 3; and in particular, q is 1 or 2,

the index r is 1, 2 or 3; and in particular, r is 1 or 2,

X⁴ is -O-, -NR⁻¹⁷ -, -S-, -S(O)-, -S(O)₂-, or a bond and preferable, X⁴ is -O- or a bond, and

R⁻¹⁷ is hydrogen, C₁-C₆ -alkyl or C₃-C₁₂ -cycloalkyl. Preferably, R⁻¹⁷ is hydrogen.

Particular combinations of q and r include moieties wherein q is 1 and r is 1, or q is 2 and r is 1.

Particular combinations of q, r and X⁴ include moieties where q is 1, r is 1 and X⁴ is -O- (oxetanyl);
q is 1, r is 1 and X⁴ is a bond (cyclopropyl); or q is 2, r is 1 and X⁴ is a bond (cy-clobutyl).

According to a preferred embodiment, R⁴⁻¹⁷ is hydrogen, halogen, C₁-C₆ -alkyl, C₃-C₁₂ -cycloalkyl-
C₆-alkyl, halogenated C₁-C₆ -alkyl, hydroxy-C₁-C₆-alkyl, C₁-C₆ -alkoxy-C₁-C₆-alkyl, optionally substituted
C₆-C₁₂ -aryl-C₁-C₆-alkyl, C₂-C₆ -alkenyl, C₂-C₆ -alkynyl, optionally substituted C₆-C₁₂ 
aryl, cyano, hydroxy, C₁-C₆ -alkoxy, halogenated C₁-C₆ -alkoxy, C₁-C₆ -hydroxyalkoxy, C₁-C₆-
alkoxy-C₁-C₆-alkoxy, C₁-C₆ -alkoxy-C₁-C₆-alkoxy, C₁-C₆ -alkoxy-C₁-C₆-alkoxy or C₆-aryl-C₁-C₆-
alkoxy.

According to a particular embodiment, R⁴⁻¹⁷ is hydrogen, halogen, C₁-C₆ -alkyl, C₃-C₁₂ -cycloalkyl-
C₁-C₆ -alkyl, halogenated C₁-C₆ -alkyl, hydroxy-C₁-C₆-alkyl, C₁-C₆ -alkoxy-C₁-C₆-alkyl, optionally substituted
C₆-aryl-C₁-C₆-alkyl, optionally substituted C₆-aryl, cyano, hydroxy, C₁-C₆ -alkoxy, halogenated C₁-C₆ -alkoxy,
C₁-C₆ -hydroxyalkoxy, C₁-C₆ -alkoxy-C₁-C₆-alkoxy or C₆-aryl-C₁-C₆-alkoxy.

According to a preferred embodiment, R⁴⁻¹⁷ is hydrogen, halogen, C₁-C₆ -alkyl, C₃-C₁₂ -cycloalkyl-Cr
C₆-alkyl, halogenated C₁-C₆ -alkyl, hydroxy-C₁-C₆-alkyl, C₁-C₆ -alkoxy-C₁-C₆-alkyl, optionally sub-
stituted C₆-C₁₂ -aryl-C₁-C₆-alkyl, C₂-C₆ -alkenyl, C₂-C₆ -alkynyl, optionally substituted C₆-C₁₂ -aryl,
cyano or optionally substituted C₃-C₁₂ -heterocyclyl.

According to a particular embodiment, R⁴⁻¹⁷ is hydrogen, halogen, C₁-C₆ -alkyl, C₃-C₁₂ -cycloalkyl-Cr
C₆-alkyl, halogenated C₁-C₆ -alkyl, hydroxy-C₁-C₆-alkyl, C₁-C₆ -alkoxy-C₁-C₆-alkyl, optionally sub-
stituted C₆-C₁₂ -aryl-C₁-C₆-alkyl, optionally substituted C₆-aryl, cyano or C₆-aryl-C₁-C₆-alkoxy.

It is in particular preferred if R⁴⁻¹⁷ is an electron withdrawing group.

In connection with R⁴⁻¹⁷ substituted C₁-C₆ -alkyl in particular includes C₁-C₆ -alkyl, especially C₁-C₄-
alkyl, substituted with 1, 2 or 3 substituents selected from the group consisting of hydroxy, C₁-C₆-
alkoxy, amino, Ci-C6-alkylamino, di-Ci-C6-alkylamino and M3-M12-heterocyclyl (e.g. morpholinyl or piperidinyl).

Preferably, R4a is hydrogen, Ci-C6-alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, 2-methyl-but-4-yl, or 2-methyl-prop-3-yl), C3-C12-cycloalkyl-Ci-C4-alkyl (e.g. cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, 1-cyclopropyl-eth-2-yl, 1-cyclopentyl-eth-2-yl, or cyclohexylmethyl), halogenated Ci-C4-alkyl (e.g. 2-fluoroethyl or 2,2,2-trifluoroethyl), amino-Ci-C4-alkyl, -CH2CN, C6-C12-aryl-Ci-C4-alkyl (e.g. benzyl), optionally substituted C3-C12-cycloalkyl (e.g. cyclopropyl or cyclobutyl), Ci-C4-alkylcarbonyl (e.g. methylcarbonyl or isopropylcarbonyl), (halogenated C1-C4-alkyl)carbonyl (e.g. fluoromethylcarbonyl, difluoromethylcarbonyl or trifluoromethylcarbonyl), C6-C12-aryloxycarbonyl (e.g. phenylcarbonyl), Ci-C4-alkoxycarbonyl (e.g. ethoxy carbonyl or tert-butyloxycarbonyl), C6-C12-aryloxycarbonyl (e.g. phenoxy carbonyl), -C(=NH)NH2, -C(=NH)HCN, Ci-Calkylsulfonyl, amino, -NO or optionally substituted M3-M12-heterocyclyl (e.g. 3-oxetany1).

More preferably, R4a is hydrogen, Ci-C6-alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, 2-methyl-but-4-yl, or 2-methyl-prop-3-yl), optionally substituted C3-C12-cycloalkyl (e.g. cyclopropyl or cyclobutyl), C3-C12-cycloalkyl-Ci-C4-alkyl (e.g. cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, 1-cyclopropyl-eth-2-yl, 1-cyclopentyl-eth-2-yl, or cyclohexylmethyl), or M3-M12-heterocyclyl (e.g. 3-oxetany1).

In particular, R4a is hydrogen, Ci-C6-alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, 2-methyl-but-4-yl, or 2-methyl-prop-3-yl), C3-C12-cycloalkyl-Ci-C4-alkyl (e.g. cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, 1-cyclopropyl-eth-2-yl, 1-cyclopentyl-eth-2-yl, or cyclohexylmethyl), or optionally substituted C3-C12-cycloalkyl (e.g. cyclopropyl or cyclobutyl).

Alternatively, R4a is optionally substituted Ci-C4-alkylene (e.g. methylene, 1,2-ethylene, or 1,3-propylene) that is bound to a carbon atom in Y1. In connection with R4a, substituted Ci-C4-alkylene in particular includes Ci-C4-alkylene substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, Ci-C4-alkyl, Ci-C4-haloalkyl, cyano, hydroxy and Ci-C4-alkoxy. In particular, R4a is Ci-C4-alkylene (e.g. methylene or 1,2-ethylene) that is bound to a carbon atom in Y1 with Y1 being optionally substituted Ci-C4-alkylene (e.g. 1,2-ethylene or 1,3-propylene) so that R4a and at least part of Y1 together with the nitrogen atom to which R4a and Y1 are bound form an N-containing heterocyclic ring having, in particular, 4, 5 or 6 ring member atoms (including the nitrogen atom). A derivative of the invention having such a ring may be represented by the following partial structure:
wherein A, R₁, W, A₁, Q, Y, R₆, n₁, n₂, X₁, R², A², R³, R⁴b, X², X³, R⁵ are as defined herein, s is 0, 1 or 2, and t is 0, 1, 2, or 3. Particular combinations of s and t include s=1, t=1; s=0, t=1; s=1, t=2; and s=0, t=2.

R⁴b is hydrogen, Cᵢ-C₆-alkyl (e.g. methyl, ethyl), halogenated Cᵢ-C₄-alkyl, hydroxy-Cᵢ-C₄-alkyl, Cᵢ-C₆-alkoxy-Cᵢ-C₄-alkyl, amino-Cᵢ-C₄-alkyl, -CH₂CN, -CHO, Cᵢ-C₄-alkylcarbonyl, (halogenated Cᵢ-C₄-alkyl)carbonyl, C₆-C₁₂ -arylcarnonyl, Cᵢ-C₄-alkoxycarbonyl, C₆-C₁₂ -arylxy carbonyl, Cᵢ-C₆-alkylaminocarbonyl, C₂-C₆-alkenyl, -C(=NH)NH₂, -C(=NH)NHCN, C₁-C₆-alkylsulfonyl, C₆-C₁₂ arylsulfonyl, amino, -NO or M₃-M₁₂-heterocyclyl.

Preferably, R⁴b is hydrogen or Cᵢ-C₆-alkyl (e.g. methyl or ethyl). In particular, R⁴b is hydrogen.

Alternatively, R⁴a, R⁴b together are optionally substituted C₂-C₆-alkylene (e.g. 1,4-butylene, 1,3-propylene, 2-fluoro-but-1,4-yylene, 1-oxo-but-1,4-ylele, 2-methyl-1,3-propylene, 2,2-dimethyl-1,3-propylene, or 2-methyl-2-hydroxy-1,3-propylene), wherein one -CH₂⁻ of C₂-C₆-alkylene may be replaced by an oxygen atom (e.g. -CH₂-CH₂-0-CH₂-CH₂-) or -NR⁺⁻.

In connection with R⁴a and R⁴b, substituted C₂-C₆-alkylene in particular includes C₂-C₆-alkylene substituted with 1 or more substituents R⁴c, R⁴d and/or R⁴e.

The compounds of the invention may therefore be represented by the following formula:

```latex
\begin{align*}
\text{R}^1 & \longrightarrow \text{W} \longrightarrow \text{A} \longrightarrow \text{Q} \longrightarrow \text{Y} \\
\text{R}^6 & \longrightarrow \text{A} \longrightarrow \text{Q} \longrightarrow \text{Y} \\
\text{R}^2 & \longrightarrow \text{A} \longrightarrow \text{Q} \longrightarrow \text{Y} \\
\text{R}^3 & \longrightarrow \text{A} \longrightarrow \text{Q} \longrightarrow \text{Y} \\
\text{R}^4 & \longrightarrow \text{A} \longrightarrow \text{Q} \longrightarrow \text{Y} \\
\text{R}^5 & \longrightarrow \text{A} \longrightarrow \text{Q} \longrightarrow \text{Y}
\end{align*}
```

wherein A, R₁, W, A₁, Q, Y, R₆, n₁, n₂, X₁, R², A², R³, Y¹, X², X³ and R⁵ are as defined herein, R⁴c and R⁴d are hydrogen, or R⁴c, R⁴d together are Cᵢ-C₅-alkylene optionally substituted with 1, 2 or 3 substituents R⁴f, wherein one -CH₂⁻ of Cᵢ-C₅-alkylene may be replaced by an oxygen atom or -NR⁺⁻.
R\textsuperscript{5} is hydrogen, halogen, C\textsubscript{1}-C\textsubscript{6} -alkyl, C\textsubscript{3}-C\textsubscript{6} -cycloalkyl-C\textsubscript{1}-C\textsubscript{4} -alkyl, halogenated C\textsubscript{1}-C\textsubscript{6} -alkyl, hydroxy-C\textsubscript{1}-C\textsubscript{4} -alkyl, C\textsubscript{1}-C\textsubscript{6} -alkoxy-C\textsubscript{1}-C\textsubscript{4} -alkyl, optionally substituted C\textsubscript{6}-C\textsubscript{12} -aryl-C\textsubscript{1}-C\textsubscript{4} -alkyl, optionally substituted C\textsubscript{6}-C\textsubscript{12} -aryl, cyano, hydroxy, C\textsubscript{1}-C\textsubscript{6} -alkoxy, halogenated C\textsubscript{1}-C\textsubscript{6} -alkoxy, C\textsubscript{1} - C\textsubscript{6} -hydroxyalkoxy, C\textsubscript{1}-C\textsubscript{6} -alkoxy-C\textsubscript{1}-C\textsubscript{4} -alkoxy or C\textsubscript{6}-C\textsubscript{12} -aryl-C\textsubscript{1}-C\textsubscript{4} -alkoxy; and in particular, R\textsuperscript{5} is hydrogen.

t is 0, 1, 2 or 3; and according to a particular embodiment, t is 1, and R\textsuperscript{8} is hydrogen, C\textsubscript{1}-C\textsubscript{6} -alkyl or C\textsubscript{3}-C\textsubscript{12} -cycloalkyl. Preferably, R\textsuperscript{8} is hydrogen.

In connection with R\textsuperscript{4} and R\textsuperscript{5} substituted C\textsubscript{6}-C\textsubscript{12} -aryl in particular includes C\textsubscript{6}-C\textsubscript{12} -aryl, such as phenyl, substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, C\textsubscript{1}-C\textsubscript{4} -alkyl, C\textsubscript{1}-C\textsubscript{4} -haloalkyl, cyano, C\textsubscript{1}-C\textsubscript{4} -alkoxy and C\textsubscript{1}-C\textsubscript{4} -haloalkoxy. The same applies to substituted C\textsubscript{6}-C\textsubscript{12} -aryl in substituted C\textsubscript{6}-C\textsubscript{12} -aryl-C\textsubscript{1}-C\textsubscript{4} -alkyl.

According to a particular embodiment R\textsuperscript{4}, R\textsuperscript{4d} together are C\textsubscript{1}-C\textsubscript{5} -alkylene optionally substituted with 1, 2 or 3 substituents R\textsuperscript{4f}, wherein one -CH\textsubscript{2} of C\textsubscript{1}-C\textsubscript{5} -alkylene may be replaced by an oxygen atom or -NR\textsuperscript{18}.

In connection with R\textsuperscript{4f}, R\textsuperscript{4d} substituted C\textsubscript{1}-C\textsubscript{5} -alkylene in particular includes C\textsubscript{1}-C\textsubscript{5} -alkylene optionally substituted with 1, 2 or 3 substituents (R\textsuperscript{4f}) selected from the group consisting of hydrogen, halogen, C\textsubscript{1}-C\textsubscript{6} -alkyl, C\textsubscript{3}-C\textsubscript{12} -cycloalkyl-C\textsubscript{1}-C\textsubscript{4} -alkyl, halogenated C\textsubscript{1}-C\textsubscript{6} -alkyl, hydroxy-C\textsubscript{1}-C\textsubscript{4} -alkyl, C\textsubscript{1}-C\textsubscript{6} -alkoxy-C\textsubscript{1}-C\textsubscript{4} -alkyl, optionally substituted C\textsubscript{6}-C\textsubscript{12} -aryl-C\textsubscript{1}-C\textsubscript{4} -alkyl, C\textsubscript{2}-C\textsubscript{6} -alkenyl, C\textsubscript{2}-C\textsubscript{6} -alkynyl, optionally substituted C\textsubscript{6}-C\textsubscript{12} -aryl, cyano, hydroxy, C\textsubscript{1}-C\textsubscript{6} -alkoxy, halogenated C\textsubscript{1}-C\textsubscript{6} -alkoxy, C\textsubscript{1}-C\textsubscript{6} -hydroxyalkoxy, C\textsubscript{1}-C\textsubscript{6} -alkoxy-C\textsubscript{1}-C\textsubscript{4} -alkoxy, C\textsubscript{6}-C\textsubscript{12} -aryl-C\textsubscript{1}-C\textsubscript{4} -alkoxy, M\textsubscript{3}-M\textsubscript{12}-heterocyclyloxy or optionally substituted M\textsuperscript{3}-M\textsubscript{12}-heterocyclyl, and more preferably hydrogen.

According to a further particular embodiment, R\textsuperscript{4e}, R\textsuperscript{4d} together with the carbon atom or the carbon atoms to which they are bound form a 3-, 4-, 5- or 6-membered ring, for example a ring comprised by the formula:
wherein \( t \) is defined as herein and \( u \) is 0, 1, 2, or 3, and \( R^{4e} \) and \( R^{4f} \) are as defined herein. Particular combinations of \( u \) and \( t \) include \( t=1 \) and \( u=0 \).

In said formulae, there may be one or more than one radical \( R^{4e} \) and/or \( R^{4f} \). More particularly, there may be up to 3 radicals \( R^{4e} \) and/or up to 3 radicals \( R^{4f} \). Preferably there is one radical \( R^{4e} \) and/or one radical \( R^{4f} \). Said formulae may thus also be depicted as follows:

In said formulae, \( e \) is 1, 2 or 3 and \( f \) is 1, 2, or 3, with \( R^{4e} \), \( R^{4f} \), \( t \) and \( u \) being as defined herein. If there is more than one radical \( R^{4e} \), these may be the same or different radicals. If there is more than one radical \( R^{4f} \), these may be the same or different radicals.

The following examples of bicyclic moieties illustrate particular combinations of \( t \), \( u \) and \( R^{4e} \), \( R^{4f} \) in the compounds of the present invention:
wherein $R^{4e}$, $R^{4f}$ are as defined herein and in particular are both hydrogen.

Compounds of the invention having the following bicyclic moiety:
wherein $R^{4e}$, $R^{4f}$ are as defined herein and in particular are both hydrogen, are particularly preferred.

$X^2$ is -0-, -NR$^{11a}$, -S-, $\cdot CR^{12a}$ or a bond. In particular, $X^2$ is not a bond. Preferably, $X^2$ is $\cdot CR^{12a}$. $X^3$ is -0-, -NR$^{11b}$, -S-, $\cdot CR^{13b}$ or a bond. Preferably, $X^3$ is a bond.

Thus, it is preferred if $X^2$ is $\cdot CR^{12a}$ and $X^3$ is a bond.

$R^{12a}$ is hydrogen, optionally substituted Ci-C6-alkyl, Ci-C6-alkylamino-Ci-C4-alkyl, di-Ci-C6-alkylamino-Ci-C4-alkyl, $M_3-M_{12}$-heterocycl-Ci-C6-alkyl, optionally substituted Ci-C6-aryl or hydroxy. Preferably, $R^{12a}$ is hydrogen or Ci-C6-alkyl.

$R^{13b}$ is hydrogen, optionally substituted Ci-C6-alkyl, Ci-C6-alkylamino-Ci-C4-alkyl, di-Ci-C6-alkylamino-Ci-C4-alkyl, $M_3-M_{12}$-heterocycl-Ci-C6-alkyl, optionally substituted Ci-C6-aryl or hydroxy. Preferably, $R^{13b}$ is hydrogen or Ci-C6-alkyl.

In connection with $R^{12a}$ and $R^{13b}$, substituted Ci-C6-alkyl in particular includes Ci-C6-alkyl substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, hydroxy, $C_1-C_4$-alkoxy and amino.

In connection with $R^{12a}$ and $R^{13b}$, substituted Ci-C6-aryl in particular includes Ci-C6-aryl, such as phenyl, substituted with 1, 2 or 3 substituents selected from the group consisting of Ci-C4-alkyl, Ci-C4-haloalkyl, cyano, Ci-C4-alkoxy and Ci-C4-haloalkoxy.

$R^{12b}$ is hydrogen or Ci-C6-alkyl. According to a particular embodiment, $R^{12b}$ is hydrogen.

$R^{13b}$ is hydrogen or Ci-C6-alkyl. According to a particular embodiment, $R^{13b}$ is hydrogen.

Alternatively, $R^{12a}$ and $R^{12b}$, or $R^{13a}$ and $R^{13b}$, together with the carbon atom to which they are attached form a carbonyl or, preferably, are optionally substituted $C_2-C_4$-alkylene (e.g. 1,3-propylene), wherein one -CH$_2$- of $C_2-C_4$-alkylene may be replaced by an oxygen atom or -NR$^{14}$.

In connection with $R^{12a}$ and $R^{12b}$, or $R^{13a}$ and $R^{13b}$, substituted $C_2-C_4$-alkylene in particular includes $C_2-C_4$-alkylene substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, Ci-C4-alkyl, Ci-C4-haloalkyl, cyano, Ci-C4-alkoxy and Ci-C4-haloalkoxy.
According to a particular embodiment, R_{12} is hydrogen or C1-C6-alkyl and R_{12b} is hydrogen or C1-C6-alkyl, or R_{13a} is hydrogen or C1-C6-alkyl and R_{13b} is hydrogen or C1-C6-alkyl.

According to a further particular embodiment, R_{12a} is hydrogen and R_{12b} is hydrogen, or R_{13a} is hydrogen and R_{13b} is hydrogen.

According to a further particular embodiment, R_{12a} and R_{12b} together are optionally substituted 1,3-propylene, or R_{13a} and R_{13b} together are optionally substituted 1,3-propylene.

R_{5} is optionally substituted C6-C12-aryl (e.g. phenyl, 2-fluorophenyl, 2-chlorophenyl, 3-fluorophenyl, 3-chlorophenyl; 3-cyanophenyl, 3-methylphenyl, 3-trifluoromethylphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 3-fluoro-5-chlorophenyl, 3-chloro-4-fluorophenyl, 2,4-dichlorophenyl or 3,4-dichlorophenyl), optionally substituted C3-C12-cycloalkyl (e.g. cyclohexyl) or optionally substituted M_{3}-M_{12}-heterocyclyl.

In connection with R_{5}, substituted C3-C12-cycloalkyl in particular includes C3-C12-cycloalkyl, such as cyclopropyl or cyclohexyl, substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, optionally substituted C1-C6-alkyl, halogenated C1-C6-alkyl, CN, hydroxy, C1-C6-alkoxy, halogenated C1-C6-alkoxy, amino, C1-C6-alkylamino, di-C1-C6-alkylamino and M_{3}-M_{12}-heterocyclyl.

In connection with R_{5}, substituted C6-C12-aryl in particular includes C6-C12-aryl, such as phenyl, substituted with 1, 2 or 3 substituents selected from the group consisting of halogen (e.g. F, Cl, Br), optionally substituted C1-C6-alkyl (e.g. methyl), halogenated C1-C6-alkyl (e.g. trifluoromethyl), CN, hydroxy, C1-C6-alkoxy (e.g. methoxy), halogenated C1-C6-alkoxy, amino, C1-C6-alkylamino, di-C1-C6-alkylamino and M_{3}-M_{12}-heterocyclyl.

In connection with R_{5}, substituted M_{3}-M_{12}-heterocyclyl in particular includes M_{3}-M_{12}-heterocyclyl substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, optionally substituted C1-C6-alkyl, halogenated C1-C6-alkyl, CN, hydroxy, C1-C6-alkoxy, halogenated C1-C6-alkoxy, amino, C1-C6-alkylamino, di-C1-C6-alkylamino and M_{3}-M_{12}-heterocyclyl.

In connection with R_{5}, M_{3}-M_{12}-heterocyclyl in particular is M_{3}-M_{12}-heteroaryl.

Preferably, R_{5} is optionally substituted C6-C12-aryl, in particular as in the compounds of the formula:
wherein \( A, R^1, W, A^1, Q, Y, R^6, n_1, n_2, X^1, R^2, A^2, R^3, Y^1, R^4a, R^4b, X^2, X^3 \) are as defined herein, and
\[ R^{f_5}, R^{f_6}, R^{f_7}, R^{f_8}, R^{f_9} \] independently are hydrogen, halogen (e.g. F, Cl or Br), optionally substituted \( \text{Ci-C}_6\)-alkyl (e.g. methyl), halogenated \( \text{Ci-C}_6\)-alkyl (e.g. trifluoromethyl), CN, hydroxy, \( \text{C}_1\)-\( \text{C}_6\)-alkoxy (e.g. methoxy), amino, \( \text{Ci-C}_6\)-alkylamino, di-\( \text{Ci-C}_6\)-alkylamino or \( \text{M}_3\)-\( \text{M}_2\)-heterocycl. Preferably, \( R^{f_5}, R^{f_6}, R^{f_7}, R^{f_8}, R^{f_9} \) independently are hydrogen, halogen (e.g. F, Cl or Br), or halogenated \( \text{Ci-C}_6\)-alkyl (e.g. trifluoromethyl).

It is also preferred if \( R^5 \) is optionally substituted \( \text{M}_3\)-\( \text{M}_2\)-heteroaryl, in particular as in the compounds of the formula:

wherein \( A, R^1, W, A^1, Q, Y, R^6, n_1, n_2, X^1, R^2, A^2, R^3, Y^1, R^4a, R^4b, X^2, X^3 \) are as defined herein, and
According to a particular embodiment, the invention relates to compounds of the formula:

wherein A, R, R², A², R³, Y¹, R⁴a, R⁴b, R⁵ are as defined herein, R⁵ preferably being optionally substituted aryl and in particular optionally substituted phenyl or optionally substituted heteroaryl and in particular optionally substituted pyridinyl as disclosed herein.

In connection with R⁸ or R¹⁶a, R¹⁶b, R¹⁶c, R¹⁶d, R¹⁶e, substituted C₁-C₆-alkyl in particular includes C₆-alkyl, especially C₅-alkyl, substituted with 1, 2 or 3 substituents selected from the group consisting of hydroxy, C₆-alkoxy, amino, C₆-alkylamino, di-C₆-alkylamino and M₃-M₁₂-heterocyclyl (e.g. morpholinyl or piperidinyl).

According to a particular embodiment, R¹⁶a, R¹⁶b, R¹⁶d, R¹⁶e are hydrogen and R¹⁶c is different from hydrogen (para-mono-substitution).

According to a further particular embodiment, R¹⁶a, R¹⁶b, R¹⁶c, R¹⁶d, R¹⁶e are hydrogen and R¹⁶b is different from hydrogen (meta-mono-substitution).

In connection with R¹⁶a, R¹⁶b, R¹⁶c, R¹⁶d, R¹⁶e, M₃-M₁₂-heterocyclyl in particular includes morpholinyl, imidazolyl and pyrazolyl.

R⁷ is hydrogen or C₆-alkyl. Preferably, R⁷ is hydrogen.

R⁸ is hydrogen, C₆-alkyl (e.g. methyl or ethyl), C₃-C₉-cycloalkyl (e.g. cyclopropyl) amino-C₆-alkyl, optionally substituted C₆-C₁₂-aryl-C₄-alkyl or M₁-M₁₂-heterocyclyl (e.g. 3-azetidinyl). Preferably, R⁸ is hydrogen or C₆-alkyl (e.g. methyl or ethyl). In particular, R⁸ is hydrogen.

According to a particular embodiment, R⁸ and R¹ together are C₄-alkylene (e.g. 1,2-ethylene or 1,3-propylene) so as that R⁸ and R¹ together with the atom in Q to which R¹ is bound and the nitrogen atom to which R⁸ is bound form an heterocyclic ring having, in particular, 4, 5 or 6 ring mem-
ber atoms (including the nitrogen atom and Q). With W and A both being a bond, such a ring may be represented by the following partial structure:

\[
\begin{array}{c}
\text{Q-N-} \\
\text{\hphantom{Q-N-}} \\
\text{\hphantom{Q-N-}} \\
\\text{\hphantom{Q-N-}} \\
\end{array}
\begin{array}{c}
\text{\hphantom{Q-N-}} \\
\\text{\hphantom{Q-N-}} \\
\\text{\hphantom{Q-N-}} \\
\\text{\hphantom{Q-N-}} \\
\end{array}
\begin{array}{c}
\text{\hphantom{Q-N-}} \\
\\text{\hphantom{Q-N-}} \\
\\text{\hphantom{Q-N-}} \\
\\text{\hphantom{Q-N-}} \\
\end{array}
\begin{array}{c}
\{\text{CH}_2\}_n \\
\text{\hphantom{Q-N-}} \\
\text{\hphantom{Q-N-}} \\
\text{\hphantom{Q-N-}} \\
\end{array}
\]

wherein Q is as defined herein (e.g. S(0)₂) and n is 0, 1, 2, 3 or 4.

R⁹ is hydrogen, Ci-C₆-alkyl, C₅-C₂-cycloalkyl-Ci-C₄-alkyl, halogenated Ci-C₄-alkyl, hydroxy-Cr C₄-alkyl, Ci-C₆-alkoxy-Ci-C₄-alkyl, amino-Ci-C₄-alkyl, -CH₂CN, C₆-Ci₂-aryl-Ci-C₄-alkyl, C₃-Ci₁₂- cycloalkyl, -CHO, Ci-C₄-alkylcarbonyl, (halogenated Ci-C₄-alkyl)carbonyl, C₆-Ci₂-arylcarbonyl, Ci-C₄-alkoxy-carbonyl, C₆-Ci₂-arylcarbonyl, Ci-C₆-alkylaminocarbonyl, C₆-Ci₂-alkylsulfonyl, Ci-C₆-alkylaminocarbonyl, C₆-Ci₂-alkylsulfonyl, amino, -NO₃ or M₁₋M₁₂⁻ heterocyclyl. Preferably, R⁹ is hydrogen or Ci-C₆-alkyl. In particular, R⁹ is hydrogen.

R⁰ is hydrogen or Ci-C₆-alkyl. Preferably, R⁰ is hydrogen.

R¹¹ is hydrogen or Ci-C₆-alkyl. Preferably, R¹¹ is hydrogen.

R¹¹ is hydrogen or Ci-C₆-alkyl. Preferably, R¹¹ is hydrogen.

R¹⁴ is hydrogen or Ci-C₆-alkyl. Preferably, R¹⁴ is hydrogen.

R¹⁵ is hydrogen or Ci-C₆-alkyl. Preferably, R¹⁵ is hydrogen.

R¹⁷ is hydrogen, Ci-C₆-alkyl or C₅-C₂-cycloalkyl. Preferably, R¹⁷ is hydrogen.

R¹⁸ is hydrogen, Ci-C₆-alkyl or C₅-C₂-cycloalkyl. Preferably, R¹⁸ is hydrogen.

30 Particular embodiments of compounds of the invention result if

A is a benzene ring
R¹ is Ci-C₆-alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, n-pentyl), C₅-C₂-cycloalkyl-Ci-C₄-alkyl (e.g. cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclopropylethyl), halogenated Ci-C₆-alkyl (e.g. 3-fluoroprop-1-yl, 3-chloroprop-1-yl or 3,3,3-trifluoroprop-1-yl), tri-(Ci-C₄-alkyl)-silyl-Ci-C₄-alkyl (e.g. trimethylsilyl), Ci-C₆-alkoxy-Ci-C₄-alkyl (e.g. ethoxyethyl), C₅-C₂-cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclohexyl), C₂-C₆-alkenyl (e.g. prop-2-en-1-yl), optionally substituted C₆-Ci₂-aryl (e.g. phenyl, 3-methylphenyl), or optionally substituted M₁₋M₁₂⁻ heterocyclyl (e.g. 2-pyridyl, 3-pyridyl, 2-F-pyridin-3-yl, 5-F-pyridin-3-yl, pyridazin-3-yl, 1-methyl-pyrrol-
3yl, 2-thienyl, 3-thienyl, 4-methyl-2-thienyl, 5-methyl-2-thienyl, 2,5-dimethyl-3-thienyl, 3-furanyl, 5-methyl-2-furanyl, 2,5-dimethyl-3-furanyl, 1,2-diazol-4-yl, 1-methyl-1,2-diazol-4-yl, 1,3-dimethyl-1,2-diazol-4-yl, 1-ethyl-1,2-diazol-4-yl, 1-difluoromethyl-1,2-diazol-4-yl, 1-methyl-3-trifluoromethyl-1,2-diazol-4-yl, 1-methyl-1,3-diazol-4-yl, 2-methyl-1,3-diazol-4-yl, 1,2-dimethyl-1,3-diazol-4-yl, 2-methyl-1,3-thiazol-5-yl, 2,4-dimethyl-1,3-thiazol-5-yl, 5-methylisoxazol-3-yl, 1-methyl-1,2,3-triazol-4-yl, 1-ethyl-1,2,3-triazol-4-yl, 1-methyl-1,2,4-triazol-1-3-yl, 3-pyrrolidinyl, 3-oxenatyl, 3-methyl-piperidinyl, 4-morpholinyl, 2,2-difluoro-1,3-benzdioxol-5-yl);

w is a bond or NR²;

10 A¹ is a bond;
Q is -SO(0)²⁻ or -C(O)-;
Y is NR² or a bond;
n¹ is 1 or 2;
n² is 1 or 2;

15 R⁶ is hydrogen, Ci-C₆-alkyl (e.g. methyl), or two radicals R⁶ together with the carbon atom to which they are attached form a carbonyl group;
X¹ is >N- or >CH₂-;
R² is hydrogen, halogen (e.g. fluorine), or -CN;
A² is -O-;

20 R³ is hydrogen or Ci-C₆-alkyl (e.g. methyl);
Y¹ is a bond or substituted Ci-C₄-alkylene (e.g. methylene, 1,2-ethylene);
R₄a is hydrogen, Ci-C₆-alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, 2-methyl-but-4-yl, 2-methyl-prop-3-yl), C₃-C₄ -cycloalkyl-Ci-C₄-alkyl (e.g. cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, 1-cyclopropyleth-2-yl, 1-cyclopentyleth-2-yl, cyclohexylmethyl), halogenated C₁-C₄-alkyl (e.g. 2-fluoroethyl, 2,2,2-trifluoroethyl), C₃-C₄ -cycloalkyl (e.g. cyclopropyl, cyclobutyl), -CHO, Ci-C₄-alkyloxycarbonyl (e.g. methylcarbonyl, ethylcarbonyl, isopropylcarbonyl), (halogenated Ci-C₄-alkyl)carbonyl (e.g. fluoromethylcarbonyl, difluoromethylcarbonyl, trifluoromethylcarbonyl, 1,1,1-trifluoropro-3-ylcarbonyl), C₆-C₁₂ -aryloxycarbonyl (e.g. phenylcarbonyl), C₁-C₄-alkoxy carbonyl (e.g. ethoxycarbonyl, tert-butyloxycarbonyl), C₆-C₁₂ -aryloxy carbonyl (e.g. phenoxy carbonyl) or optionally substituted M₁-M₁₂-heterocyclyl (e.g. 3-oxyanil, 3-cyanooxyanil); or
R₄b is optionally substituted Ci-C₄-alkylene that is bound to a carbon atom in Y¹ (e.g. methylene, 1,2-ethylene, 1,3-propylene);

35 R₄b is hydrogen or Ci-C₆-alkyl (e.g. methyl, ethyl); or
R₅, R₄b together are optionally substituted C₂-C₆-alkylene (e.g. 1,3-propylene, 1,4-butylene, 2-methyl-1,3-propylene, 2,2-dimethyl-1,3-propylene, 2-methyl-2-hydroxy-1,3-propylene, 2-fluoro-but-1,4-ylen, 1-oxo-but-1,4-ylen, -CH₂-cycloprop-1,2-ylen-CH₂-) wherein one -CH₂- of C₂-C₆-alkylene may be replaced by an oxygen atom (e.g. -CH₂-CH₂ -O-CH₂-CH₂-);

X² is >CR¹²R¹²b;
X³ is a bond;
R^5 is optionally substituted phenyl (e.g. phenyl, 2-fluorophenyl, 2-chlorophenyl, 3-fluorophenyl, 3-chlorophenyl, 3-trifluoromethylphenyl, 3-cyanophenyl, 3-methylphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 3-fluoro-5-chlorophenyl, 3-chloro-4-fluorophenyl, 3,4-dichlorophenyl, 2,4-dichlorophenyl) or optionally substituted C_3-C_12-cycloalkyl (e.g. cyclohexyl);

R^7 is hydrogen or Ci-C_6-alkyl (e.g. methyl);
R^8 is hydrogen, Ci-C_6-alkyl (e.g. methyl or ethyl), or C_3-C_12-cycloalkyl (e.g. cyclopropyl); or
R^8, R^1 together are Ci-C_4-alkylene (e.g. 1,3-propylene);

R^{12a} is hydrogen, C_1-C_6-alkyl (e.g. methyl or ethyl);
R^{12b} is hydrogen;
R^{12a}, R^{12b} together are optionally substituted C_2-C_4-alkylene (e.g. 1,3-propylene).

Further particular embodiments of compounds of the invention result if

A is a benzene ring
R^1 is Ci-C_6-alkyl (e.g. ethyl, n-propyl), C_3-C_12-cycloalkyl-Ci-C_4-alkyl (e.g. cyclopropylmethyl), or optionally substituted M_2-M_{12}-heterocycl (e.g. 3 e.g. 1-methyl-1,2-diazol-4-yl, 1-methyl-1,3-diazol-4-yl, 1-methyl-1,2,3-triazol-4-yl, 1-ethyl-1,2,3-triazol-4-yl, 2-F-pyridin-3-yl, 5-F-pyridin-3-yl, pyridazin-3-yl);

W is a bond;
A^1 is a bond;
Q is -S(0) \_2;
Y is NR^8;
n_1 is 1;
n_2 is 1;
R^6 is hydrogen;
X^1 is >N- or >CH-;
R^2 is hydrogen or halogen (e.g. fluorine);

A^2 is -O-;
R^3 is hydrogen;
Y^1 is a bond;
R^{12b} is hydrogen, Ci-C_6-alkyl (e.g. methyl, ethyl, n-propyl), C_3-C_12-cycloalkyl-Ci-C_4-alkyl (e.g. cyclopropylmethyl) or C_3-C_12-cycloalkyl (e.g. cyclobutyl);

R^{12b} is hydrogen or Ci-C_6-alkyl (e.g. ethyl); or
R^{12b}, R^{12b} together are C_2-C_6-alkylene (e.g. 1,3-propylene);
X^2 is >CR^{12a}R^{12b};
X^3 is a bond;

R^5 is optionally substituted phenyl (e.g. phenyl);
R^8 is hydrogen, or
R^{12a} is hydrogen;
Further particular compounds of the present invention are the individual aminochromane, amino-

[Diagram of chemical structure]

Further particular compounds of the present invention are the individual aminochromane, aminothiochromane and amino-1,2,3,4-tetrahydroquinoline derivatives of the formula (Id) as listed in the following tables 1 to 24 and physiologically tolerated salts thereof:

Table 1

| Compounds of the formula (la) wherein R^6 is as defined herein and in particular represents H, -A^2- is as defined herein and in particular represents -O-, -Y^1- is as defined herein and in particular represents a bond, R^2 is hydrogen, R^3 is as defined herein and in particular represents hydrogen, R^16 is hydrogen and the combination of R^1, -X^1-, nl, n2, >CR^12^bR^12^b, R^4^b, R^4^b for a compound in each case corresponds to one line of Table A (A-1 to A-88). |

Table 2

| Compounds of the formula (la) wherein R^6 is as defined herein and in particular represents H, -A^2- is as defined herein and in particular represents -O-, -Y^1- is as defined herein and in particular represents a bond, R^2 is hydrogen, R^3 is as defined herein and in particular represents hydrogen, R^16 is 3-F and the combination of R^1, -X^1-, nl, n2, >CR^12^bR^12^b, R^4^b, R^4^b for a compound in each case corresponds to one line of Table A (A-1 to A-88). |

Table 3

| Compounds of the formula (la) wherein R^6 is as defined herein and in particular represents H, -A^2- is as defined herein and in particular represents -O-, -Y^1- is as defined herein and in particular represents a bond, R^2 is hydrogen, R^3 is as defined herein and in particular represents hydrogen, R^16 is 3-Cl and the combination of R^1, -X^1-, nl, n2, >CR^12^bR^12^b, R^4^b, R^4^b for a compound in each case corresponds to one line of Table A (A-1 to A-88). |

Table 4

| Compounds of the formula (la) wherein R^6 is as defined herein and in particular represents H, -A^2- is as defined herein and in particular represents -O-, -Y^1- is as defined herein and in particular represents a bond, R^2 is hydrogen, R^3 is as defined herein and in particular represents hydrogen, R^16 is
3-CF₃ and the combination of R¹, -X¹, nl, n₂, >CR¹²⁸R₁₂, R⁴₂, R⁴ᵇ for a compound in each case corresponds to one line of Table A (A-1 to A-88).

Table 5
Compounds of the formula (la) wherein R⁶ is as defined herein and in particular represents H, -A²⁻ is as defined herein and in particular represents -0⁻, -Y¹⁻ is as defined herein and in particular represents a bond, R² is hydrogen, R³ is as defined herein and in particular represents hydrogen, R¹₆ is 4-F and the combination of R¹, -X¹, nl, n₂, >CR¹²⁸R₁₂, R⁴₂, R⁴ᵇ for a compound in each case corresponds to one line of Table A (A-1 to A-88).

Table 6
Compounds of the formula (la) wherein R⁶ is as defined herein and in particular represents H, -A²⁻ is as defined herein and in particular represents -0⁻, -Y¹⁻ is as defined herein and in particular represents a bond, R² is hydrogen, R³ is as defined herein and in particular represents hydrogen, R¹₆ is 4-Cl and the combination of R¹, -X¹, nl, n₂, >CR¹²⁸R₁₂, R⁴₂, R⁴ᵇ for a compound in each case corresponds to one line of Table A (A-1 to A-88).

Table 7
Compounds of the formula (la) wherein R⁶ is as defined herein and in particular represents H, -A²⁻ is as defined herein and in particular represents -0⁻, -Y¹⁻ is as defined herein and in particular represents a bond, R² is 5-F, R³ is as defined herein and in particular represents hydrogen, R¹₆ is hydrogen and the combination of R¹, -X¹, nl, n₂, >CR¹²⁸R₁₂, R⁴₂, R⁴ᵇ for a compound in each case corresponds to one line of Table A (A-1 to A-88).

Table 8
Compounds of the formula (la) wherein R⁶ is as defined herein and in particular represents H, -A²⁻ is as defined herein and in particular represents -0⁻, -Y¹⁻ is as defined herein and in particular represents a bond, R² is 5-F, R³ is as defined herein and in particular represents hydrogen, R¹₆ is 3-F and the combination of R¹, -X¹, nl, n₂, >CR¹²⁸R₁₂, R⁴₂, R⁴ᵇ for a compound in each case corresponds to one line of Table A (A-1 to A-88).

Table 9
Compounds of the formula (la) wherein R⁶ is as defined herein and in particular represents H, -A²⁻ is as defined herein and in particular represents -0⁻, -Y¹⁻ is as defined herein and in particular represents a bond, R² is 5-F, R³ is as defined herein and in particular represents hydrogen, R¹₆ is 3-Cl and the combination of R¹, -X¹, nl, n₂, >CR¹²⁸R₁₂, R⁴₂, R⁴ᵇ for a compound in each case corresponds to one line of Table A (A-1 to A-88).

Table 10
Compounds of the formula (la) wherein R⁶ is as defined herein and in particular represents H, -A²⁻ is as defined herein and in particular represents -0⁻, -Y¹⁻ is as defined herein and in particular represents a bond, R² is 5-F, R³ is as defined herein and in particular represents hydrogen, R¹₆ is 3-CF₃
and the combination of $R^1$, $-X^1$, nl, $n_2$, $>CR^{12}R^{12b}$, $R^{4a}$, $R^{4b}$ for a compound in each case corresponds to one line of Table A (A-1 to A-88).

Table 11
Compounds of the formula (la) wherein $R^6$ is as defined herein and in particular represents H, $-A^2$- is as defined herein and in particular represents $-O-$, $-Y^1$- is as defined herein and in particular represents a bond, $R^2$ is 5-F, $R^3$ is as defined herein and in particular represents hydrogen, $R^{16}$ is 4-F and the combination of $R^1$, $-X^1$, nl, $n_2$, $>CR^{12}R^{12b}$, $R^{4a}$, $R^{4b}$ for a compound in each case corresponds to one line of Table A (A-1 to A-88).

Table 12
Compounds of the formula (la) wherein $R^6$ is as defined herein and in particular represents H, $-A^2$- is as defined herein and in particular represents a bond, $R^2$ is 5-F, $R^3$ is as defined herein and in particular represents hydrogen, $R^{16}$ is 4-Cl and the combination of $R^1$, $-X^1$, nl, $n_2$, $>CR^{12}R^{12b}$, $R^{4a}$, $R^{4b}$ for a compound in each case corresponds to one line of Table A (A-1 to A-88).

Table 13
Compounds of the formula (la) wherein $R^6$ is as defined herein and in particular represents H, $-A^2$- is as defined herein and in particular represents a bond, $R^2$ is 7-F, $R^3$ is as defined herein and in particular represents hydrogen, $R^{16}$ is hydrogen and the combination of $R^1$, $-X^1$, nl, $n_2$, $>CR^{12}R^{12b}$, $R^{4a}$, $R^{4b}$ for a compound in each case corresponds to one line of Table A (A-1 to A-88).

Table 14
Compounds of the formula (la) wherein $R^6$ is as defined herein and in particular represents H, $-A^2$- is as defined herein and in particular represents a bond $R^2$ is 7-F, $R^3$ is as defined herein and in particular represents hydrogen, $R^{16}$ is 3-F and the combination of $R^1$, $-X^1$, nl, $n_2$, $>CR^{12}R^{12b}$, $R^{4a}$, $R^{4b}$ for a compound in each case corresponds to one line of Table A (A-1 to A-88).

Table 15
Compounds of the formula (la) wherein $R^6$ is as defined herein and in particular represents H, $-A^2$- is as defined herein and in particular represents a bond, $R^2$ is 7-F, $R^3$ is as defined herein and in particular represents hydrogen, $R^{16}$ is 3-Cl and the combination of $R^1$, $-X^1$, nl, $n_2$, $>CR^{12}R^{12b}$, $R^{4a}$, $R^{4b}$ for a compound in each case corresponds to one line of Table A (A-1 to A-88).

Table 16
Compounds of the formula (la) wherein $R^6$ is as defined herein and in particular represents H, $-A^2$- is as defined herein and in particular represents a bond, $R^2$ is 7-F, $R^3$ is as defined herein and in particular represents hydrogen, $R^{16}$ is 3-CF$_3$. 


and the combination of $R^1$, $X^1$, $n_2$, $\text{CR}^{12R}X^{12b}$, $R^{4a}$, $R^{4b}$ for a compound in each case corresponds to one line of Table A (A-1 to A-88).

Table 17

| Compounds of the formula (la) wherein $R^6$ is as defined herein and in particular represents $H$, $-A^2$ is as defined herein and in particular represents $-0$, $-Y^1$ is as defined herein and in particular represents a bond, $R^2$ is 7-F, $R^3$ is as defined herein and in particular represents hydrogen, $R^{16}$ is 4-F and the combination of $R^1$, $-X^1$, $n_2$, $\text{CR}^{12R}X^{12b}$, $n_1$, $n_2$, $R^{4a}$, $R^{4b}$ for a compound in each case corresponds to one line of Table A (A-1 to A-88). |
| Table 18 |

| Compounds of the formula (la) wherein $R^6$ is as defined herein and in particular represents $H$, $-A^2$ is as defined herein and in particular represents $-0$, $-Y^1$ is as defined herein and in particular represents a bond, $R^2$ is 7-F, $R^3$ is as defined herein and in particular represents hydrogen, $R^{16}$ is 4-Cl and the combination of $R^1$, $-X^1$, $n_1$, $n_2$, $\text{CR}^{12R}X^{12b}$, $R^{4a}$, $R^{4b}$ for a compound in each case corresponds to one line of Table A (A-1 to A-88). |
| Table 19 |

| Compounds of the formula (la) wherein $R^6$ is as defined herein and in particular represents $H$, $-A^2$ is as defined herein and in particular represents $-0$, $-Y^1$ is as defined herein and in particular represents a bond, $R^2$ is 8-F, $R^3$ is as defined herein and in particular represents hydrogen, $R^{16}$ is 4-Cl and the combination of $R^1$, $-X^1$, $n_2$, $\text{CR}^{12R}X^{12b}$, $n_2$, $R^{4a}$, $R^{4b}$ for a compound in each case corresponds to one line of Table A (A-1 to A-88). |
| Table 20 |

| Compounds of the formula (la) wherein $R^6$ is as defined herein and in particular represents $H$, $-A^2$ is as defined herein and in particular represents $-0$, $-Y^1$ is as defined herein and in particular represents a bond, $R^2$ is 8-F, $R^3$ is as defined herein and in particular represents hydrogen, $R^{16}$ is 3-F and the combination of $R^1$, $-X^1$, $\text{CR}^{12R}X^{12b}$, $n_1$, $n_2$, $R^{4a}$, $R^{4b}$ for a compound in each case corresponds to one line of Table A (A-1 to A-88). |
| Table 21 |

| Compounds of the formula (la) wherein $R^6$ is as defined herein and in particular represents $H$, $-A^2$ is as defined herein and in particular represents $-0$, $-Y^1$ is as defined herein and in particular represents a bond, $R^2$ is 8-F, $R^3$ is as defined herein and in particular represents hydrogen, $R^{16}$ is 3-Cl and the combination of $R^1$, $-X^1$, $n_2$, $\text{CR}^{12R}X^{12b}$, $R^{4a}$, $R^{4b}$ for a compound in each case corresponds to one line of Table A (A-1 to A-88). |
| Table 22 |

| Compounds of the formula (la) wherein $R^6$ is as defined herein and in particular represents $H$, $-A^2$ is as defined herein and in particular represents $-0$, $-Y^1$ is as defined herein and in particular represents a bond, $R^2$ is 8-F, $R^3$ is as defined herein and in particular represents hydrogen, $R^{16}$ is 3-CF$_3$ |
and the combination of \( R_1 \), \(-X_1\), n1, n2, \( >CR^{12b}R^{12b}\), \( R^{4a}, R^{4b}\) for a compound in each case corresponds to one line of Table A (A-1 to A-88).

Table 23
Compounds of the formula (la) wherein \( R^6\) is as defined herein and in particular represents H, \(-A^2\) is as defined herein and in particular represents a bond, \( R^2\) is 8-F, \( R^3\) is as defined herein and in particular represents hydrogen, \( R^{16}\) is 4-F and the combination of \( R_1 \), \(-X_1\), n1, n2, \( >CR^{12b}R^{12b}\), \( R^{4a}, R^{4b}\) for a compound in each case corresponds to one line of Table A (A-1 to A-88).

<table>
<thead>
<tr>
<th>R^1</th>
<th>-X^1-</th>
<th>n1</th>
<th>n2</th>
<th>&gt;CR^{12b}R^{12b}</th>
<th>R^{4a}, R^{4b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-1</td>
<td></td>
<td>1</td>
<td>1</td>
<td>-CH_2^-</td>
<td>H, H</td>
</tr>
<tr>
<td>A-2</td>
<td>&gt;N-</td>
<td>1</td>
<td>1</td>
<td>-CH_2^-</td>
<td>H, H</td>
</tr>
<tr>
<td>A-3</td>
<td></td>
<td>1</td>
<td>1</td>
<td>-CH_2^-</td>
<td>H, H</td>
</tr>
<tr>
<td>A-4</td>
<td>&gt;N-</td>
<td>1</td>
<td>1</td>
<td>-CH_2^-</td>
<td>H, H</td>
</tr>
<tr>
<td>A-5</td>
<td></td>
<td>1</td>
<td>1</td>
<td>-CH_2^-</td>
<td>H, H</td>
</tr>
<tr>
<td></td>
<td>R(^1)</td>
<td>- X(^1) -</td>
<td>n1</td>
<td>n2</td>
<td>&gt;CR(^{12a})R(^{12b})</td>
</tr>
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</tr>
<tr>
<td>A-6.</td>
<td><img src="image" alt="Pyridine" /></td>
<td>&gt;N-</td>
<td>1</td>
<td>1</td>
<td>-CH(_2)-</td>
</tr>
<tr>
<td>A-7.</td>
<td><img src="image" alt="Pyrazole" /></td>
<td>&gt;N-</td>
<td>1</td>
<td>1</td>
<td>-CH(_2)-</td>
</tr>
<tr>
<td>A-8.</td>
<td><img src="image" alt="Pyrazole" /></td>
<td>&gt;N-</td>
<td>1</td>
<td>1</td>
<td>-CH(_2)-</td>
</tr>
<tr>
<td>A-9.</td>
<td><img src="image" alt="Pyrazole" /></td>
<td>&gt;N-</td>
<td>1</td>
<td>1</td>
<td>-CH(_2)-</td>
</tr>
<tr>
<td>A-10.</td>
<td><img src="image" alt="Pyrazole" /></td>
<td>&gt;N-</td>
<td>1</td>
<td>1</td>
<td>-CH(_2)-</td>
</tr>
<tr>
<td>A-11.</td>
<td><img src="image" alt="Pyrazole" /></td>
<td>&gt;N-</td>
<td>1</td>
<td>1</td>
<td>-CH(_2)-</td>
</tr>
<tr>
<td>R¹</td>
<td>- X¹-</td>
<td>n1</td>
<td>n2</td>
<td>&gt;CR₁²R₂²b</td>
<td>R₄a, R₅b</td>
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</tr>
<tr>
<td>A-12.</td>
<td><img src="triangle" alt="Image" /></td>
<td>&gt;CH⁻</td>
<td>1</td>
<td>1</td>
<td>-CH₂⁻</td>
</tr>
<tr>
<td>A-13.</td>
<td><img src="square" alt="Image" /></td>
<td>&gt;CH⁻</td>
<td>1</td>
<td>1</td>
<td>-CH₂⁻</td>
</tr>
<tr>
<td>A-14.</td>
<td><img src="circle" alt="Image" /></td>
<td>&gt;CH⁻</td>
<td>1</td>
<td>1</td>
<td>-CH₂⁻</td>
</tr>
<tr>
<td>A-15.</td>
<td><img src="pentagon" alt="Image" /></td>
<td>&gt;CH⁻</td>
<td>1</td>
<td>1</td>
<td>-CH₂⁻</td>
</tr>
<tr>
<td>A-16.</td>
<td><img src="hexagon" alt="Image" /></td>
<td>&gt;CH⁻</td>
<td>1</td>
<td>1</td>
<td>-CH₂⁻</td>
</tr>
<tr>
<td>A-17.</td>
<td><img src="octagon" alt="Image" /></td>
<td>&gt;CH⁻</td>
<td>1</td>
<td>1</td>
<td>-CH₂⁻</td>
</tr>
<tr>
<td>A-18.</td>
<td><img src="diamond" alt="Image" /></td>
<td>&gt;CH⁻</td>
<td>1</td>
<td>1</td>
<td>-CH₂⁻</td>
</tr>
<tr>
<td>A-19.</td>
<td><img src="triangle" alt="Image" /></td>
<td>&gt;CH⁻</td>
<td>1</td>
<td>1</td>
<td>-CH₂⁻</td>
</tr>
<tr>
<td>R&lt;sup&gt;1&lt;/sup&gt;</td>
<td>- X&lt;sup&gt;1&lt;/sup&gt; -</td>
<td>n&lt;sub&gt;1&lt;/sub&gt;</td>
<td>n&lt;sub&gt;2&lt;/sub&gt;</td>
<td>&gt;CR&lt;sup&gt;12a&lt;/sup&gt;R&lt;sup&gt;12b&lt;/sup&gt;</td>
<td>R&lt;sup&gt;4a&lt;/sup&gt;, R&lt;sup&gt;4b&lt;/sup&gt;</td>
</tr>
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<tr>
<td>A-20.</td>
<td>&gt;CH-</td>
<td>1</td>
<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-H, H</td>
</tr>
<tr>
<td>A-21.</td>
<td>&gt;CH-</td>
<td>1</td>
<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>H, H</td>
</tr>
<tr>
<td>A-22.</td>
<td>&gt;CH-</td>
<td>1</td>
<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>H, H</td>
</tr>
<tr>
<td>A-23.</td>
<td>&gt;N-</td>
<td>1</td>
<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;3&lt;/sub&gt;, H</td>
</tr>
<tr>
<td>A-24.</td>
<td>&gt;N-</td>
<td>1</td>
<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;3&lt;/sub&gt;, H</td>
</tr>
<tr>
<td>A-25.</td>
<td>&gt;N-</td>
<td>1</td>
<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;3&lt;/sub&gt;, H</td>
</tr>
<tr>
<td>A-26.</td>
<td>&gt;N-</td>
<td>1</td>
<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;3&lt;/sub&gt;, H</td>
</tr>
<tr>
<td>A-27.</td>
<td>&gt;N-</td>
<td>1</td>
<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;3&lt;/sub&gt;, H</td>
</tr>
<tr>
<td>R¹</td>
<td>- X¹-</td>
<td>n¹</td>
<td>n²</td>
<td>&gt; CR¹²⁺R¹²⁻</td>
<td>R₄⁻, R₄⁻⁺</td>
</tr>
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<tr>
<td>A-28.</td>
<td><img src="pyridine" alt="Image" /></td>
<td>&gt;N-</td>
<td>1</td>
<td>1</td>
<td>-CH₂⁻</td>
</tr>
<tr>
<td>A-29.</td>
<td><img src="pyrrole" alt="Image" /></td>
<td>&gt;N-</td>
<td>1</td>
<td>1</td>
<td>-CH₂⁻</td>
</tr>
<tr>
<td>A-30.</td>
<td><img src="pyrrole" alt="Image" /></td>
<td>&gt;N-</td>
<td>1</td>
<td>1</td>
<td>-CH₂⁻</td>
</tr>
<tr>
<td>A-31.</td>
<td><img src="pyrrole" alt="Image" /></td>
<td>&gt;N-</td>
<td>1</td>
<td>1</td>
<td>-CH₂⁻</td>
</tr>
<tr>
<td>A-32.</td>
<td><img src="pyrrole" alt="Image" /></td>
<td>&gt;N-</td>
<td>1</td>
<td>1</td>
<td>-CH₂⁻</td>
</tr>
<tr>
<td>A-33.</td>
<td><img src="pyrrole" alt="Image" /></td>
<td>&gt;N-</td>
<td>1</td>
<td>1</td>
<td>-CH₂⁻</td>
</tr>
<tr>
<td>R^1</td>
<td>-X^1-</td>
<td>n1</td>
<td>n2</td>
<td>&gt;CR^{12a}R^{12b}</td>
<td>R^{4a}, R^{4b}</td>
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<tr>
<td>A-34.</td>
<td><img src="image1.png" alt="Image" /></td>
<td>&gt;CH-</td>
<td>1</td>
<td>1</td>
<td>-CH_2-</td>
</tr>
<tr>
<td>A-35.</td>
<td><img src="image2.png" alt="Image" /></td>
<td>&gt;CH-</td>
<td>1</td>
<td>1</td>
<td>-CH_2-</td>
</tr>
<tr>
<td>A-36.</td>
<td><img src="image3.png" alt="Image" /></td>
<td>&gt;CH-</td>
<td>1</td>
<td>1</td>
<td>-CH_2-</td>
</tr>
<tr>
<td>A-37.</td>
<td><img src="image4.png" alt="Image" /></td>
<td>&gt;CH-</td>
<td>1</td>
<td>1</td>
<td>-CH_2-</td>
</tr>
<tr>
<td>A-38.</td>
<td><img src="image5.png" alt="Image" /></td>
<td>&gt;CH-</td>
<td>1</td>
<td>1</td>
<td>-CH_2-</td>
</tr>
<tr>
<td>A-39.</td>
<td><img src="image6.png" alt="Image" /></td>
<td>&gt;CH-</td>
<td>1</td>
<td>1</td>
<td>-CH_2-</td>
</tr>
<tr>
<td>A-40.</td>
<td><img src="image7.png" alt="Image" /></td>
<td>&gt;CH-</td>
<td>1</td>
<td>1</td>
<td>-CH_2-</td>
</tr>
<tr>
<td>A-41.</td>
<td><img src="image8.png" alt="Image" /></td>
<td>&gt;CH-</td>
<td>1</td>
<td>1</td>
<td>-CH_2-</td>
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<tr>
<td>R&lt;sup&gt;1&lt;/sup&gt;</td>
<td>- X&lt;sup&gt;L&lt;/sup&gt;</td>
<td>n1</td>
<td>n2</td>
<td>&gt;CR&lt;sup&gt;12&lt;/sup&gt;R&lt;sup&gt;12&lt;/sup&gt;</td>
<td>R&lt;sup&gt;4a&lt;/sup&gt;, R&lt;sup&gt;4b&lt;/sup&gt;</td>
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<tr>
<td>A-42.</td>
<td>&gt;CH-</td>
<td>1</td>
<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;3&lt;/sub&gt;, H</td>
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<tr>
<td>A-43.</td>
<td>&gt;CH-</td>
<td>1</td>
<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;3&lt;/sub&gt;, H</td>
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<tr>
<td>A-44.</td>
<td>&gt;CH-</td>
<td>1</td>
<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;3&lt;/sub&gt;, H</td>
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<tr>
<td>A-45.</td>
<td>&gt;N-</td>
<td>1</td>
<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;-</td>
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</tr>
<tr>
<td>A-46.</td>
<td>&gt;N-</td>
<td>1</td>
<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;-</td>
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<tr>
<td>A-47.</td>
<td>&gt;N-</td>
<td>1</td>
<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;-</td>
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<tr>
<td>A-48.</td>
<td>&gt;N-</td>
<td>1</td>
<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;-</td>
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</tr>
<tr>
<td>A-49.</td>
<td>&gt;N-</td>
<td>1</td>
<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;-</td>
</tr>
<tr>
<td>R&lt;sup&gt;1&lt;/sup&gt;</td>
<td>- X&lt;sup&gt;1&lt;/sup&gt;</td>
<td>n1</td>
<td>n2</td>
<td>&gt;CR&lt;sup&gt;12b&lt;/sup&gt;R&lt;sup&gt;12b&lt;/sup&gt;</td>
<td>R&lt;sup&gt;4b&lt;/sup&gt;, R&lt;sup&gt;4b&lt;/sup&gt;</td>
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<tr>
<td>A-50.</td>
<td><img src="image1.png" alt="Image" /></td>
<td>1</td>
<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;-</td>
</tr>
<tr>
<td>A-51.</td>
<td><img src="image2.png" alt="Image" /></td>
<td>1</td>
<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;-</td>
</tr>
<tr>
<td>A-52.</td>
<td><img src="image3.png" alt="Image" /></td>
<td>1</td>
<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;-</td>
</tr>
<tr>
<td>A-53.</td>
<td><img src="image4.png" alt="Image" /></td>
<td>1</td>
<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;-</td>
</tr>
<tr>
<td>A-54.</td>
<td><img src="image5.png" alt="Image" /></td>
<td>1</td>
<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;-</td>
</tr>
<tr>
<td>A-55.</td>
<td><img src="image6.png" alt="Image" /></td>
<td>1</td>
<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;-</td>
</tr>
<tr>
<td>R¹</td>
<td>- X¹ -</td>
<td>n1</td>
<td>n2</td>
<td>&gt;CR¹₂₆R¹₂₇</td>
<td>R⁴₆, R⁴₇</td>
</tr>
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<td>-----</td>
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<td>A-56.</td>
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<td>-(CH₂)₃⁻</td>
</tr>
<tr>
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<td>1</td>
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<td>-CH₂⁻</td>
<td>-(CH₂)₃⁻</td>
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<td>-(CH₂)₃⁻</td>
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<td>-CH₂⁻</td>
<td>-(CH₂)₃⁻</td>
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<td>1</td>
<td>-CH₂⁻</td>
<td>-(CH₂)₃⁻</td>
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<td>n2</td>
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<td>A-64.</td>
<td><img src="image" alt="Pyrazole" /></td>
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<td><img src="image" alt="Cyclopropyl" /></td>
<td>&gt;N-</td>
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<td>A-68.</td>
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<td>A-69.</td>
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<td>1</td>
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<td>A-70.</td>
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<td>1</td>
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<td>A-71.</td>
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<td>1</td>
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<td></td>
<td>R&lt;sup&gt;1&lt;/sup&gt;</td>
<td>- X&lt;sup&gt;1&lt;/sup&gt;-</td>
<td>n1</td>
<td>n2</td>
<td>&gt;CR&lt;sup&gt;12a&lt;/sup&gt;R&lt;sup&gt;12b&lt;/sup&gt;</td>
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<td>A-72.</td>
<td><img src="image" alt="Pyridine" /></td>
<td>&gt;N-</td>
<td>1</td>
<td>1</td>
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<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
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<td>A-75.</td>
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<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
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<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
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<td>n1</td>
<td>n2</td>
<td>&gt;CR&lt;sup&gt;12b&lt;/sup&gt;R&lt;sup&gt;12b&lt;/sup&gt;</td>
<td>R&lt;sup&gt;4a&lt;/sup&gt;, R&lt;sup&gt;4b&lt;/sup&gt;</td>
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<tr>
<td>A-78.</td>
<td>&gt;CH-</td>
<td>1</td>
<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
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<tr>
<td>A-79.</td>
<td>&gt;CH-</td>
<td>1</td>
<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;-</td>
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<td>A-80.</td>
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<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;-</td>
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<td>A-81.</td>
<td>&gt;CH-</td>
<td>1</td>
<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;-</td>
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<td>A-82.</td>
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<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
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<td>A-83.</td>
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<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;-</td>
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<td>A-84.</td>
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<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;-</td>
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<td>A-85.</td>
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<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;-</td>
</tr>
<tr>
<td>R&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>n1</td>
<td>n2</td>
<td>&gt;CR&lt;sub&gt;12&lt;/sub&gt;R&lt;sup&gt;4b&lt;/sup&gt;</td>
<td>R&lt;sup&gt;4a&lt;/sup&gt;, R&lt;sup&gt;4b&lt;/sup&gt;</td>
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<td>A-86.</td>
<td>&gt;CH-</td>
<td>1</td>
<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;-</td>
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<tr>
<td>A-87.</td>
<td>&gt;CH-</td>
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<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;-</td>
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<tr>
<td>A-88.</td>
<td>&gt;CH-</td>
<td>1</td>
<td>1</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;-</td>
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</table>

Still further particular compounds of the present invention are the compounds disclosed in preparation examples and physiologically tolerated salts thereof. These include for each preparation example the exemplified compound as well as the corresponding free base and any other physiologically tolerated salts of the free base (if the exemplified compound is a salt), or any physiologically tolerated salt of the free base (if the exemplified compound is a free base). These further include enantiomers, diastereomers, tautomers and any other isomeric forms of said compounds, be they explicitly or implicitly disclosed.

The compounds of the formula (I) can be prepared by analogy to methods which are well known in the art. Suitable methods for the preparation of compounds of formula (I) are outlined in the following schemes.

The process depicted in scheme 1 is useful for obtaining aminochromanes of general formula 5, wherein X<sup>4</sup> is -0-.

Scheme 1:
As shown in scheme 1, the compound of general formula 1 can be transferred into the corresponding hydroxylamine 2 (e.g. in presence of NH₂OH HCl). The hydroxyl group can be converted to a leaving group (e.g. tosyl or mesyl) to yield compounds of the general formula 3. Compounds 3 readily undergo Neber rearrangement in the presence of a base (e.g. NaOEt, J. Med. Chem. 1988, 31, 2178) followed by protection with a suitable protecting group L² (e.g. L² = COOEt) to give the compound of general formula 5.

In scheme 1, the variables R² and R³ are as defined herein and L¹ is a suitable protecting group (e.g. L¹ = Me).

Compounds of the general formula 1 are also readily accessible from common bulk chemicals as described in scheme 2. The process depicted in scheme 2 is useful for obtaining aminochromanes of general formula 1, wherein X⁴ is -O- and L¹ is a suitable protecting group (e.g. L¹ = Me).

Scheme 2:

Phenols of the general formula 1-1 can be reacted with 3-halogenated carboxylic acids like 1-2 in presence of a base as described in the literature (e.g. potassium hydroxide, sodium hydrogen carbonate, J. Med. Chem. 1982, 25, 393) to give compounds of the general formula 1-3. In presence of an acid these compounds undergo acylation reactions to form compounds of the general formula 1 (e.g. polyphosphoric acid, J. Med. Chem. 1982, 25, 393).

The process depicted in scheme 3 is useful for obtaining aminochromanes, wherein X¹ is >N-, X⁴ is -O-, Y is -NR²-, and Q is -S(0)₂-.
Scheme 3:

Aminochromanes of the general formula 5 can be reacted with a Grignard reagent to give the alcohols of the general formula 6. In presence of an acid (e.g. aqueous hydrochloric acid) these alcohols undergo elimination to the corresponding alkenes of general formula 7. Reduction of compounds of type 7 (e.g. by hydrogenation with H₂ and Pd/C in presence of an acid (e.g. ammonium formiate)) leads to aminochromanes of the general formula 8. The free phenols 9 can be accessed via removal of the protecting group L₁ (e.g. for L₁ = Me by treating compounds 8 with boron tribromide). The phenols of general formula 9 can be transferred into the triflates 10 in presence of trifluoromethanesulfonic anhydride or 2-[N,N-Bis(trifluoromethylsulfonyl)amino]-5-chloropyridine. As described in the literature (e.g. Chem. Sci. 2011, 2, 27-50) inflate 10 can undergo a Buchwald-Hartwig amination with a cyclic amine in the presence of a palladium source (e.g. Pd(II) acetate), a ligand (e.g. dicyclohexyl(2',4',6'-triisopropyl-[1,r-biphenyl]-2-yl)phosphine) and a base (e.g. cesium carbonate) to yield compounds of the general formula 11. Alternatively to the triflates 10 the corresponding nonaflates or bromides can be used to prepare compound 11. Deprotection of the Boc-group in presence of an acid (e.g. trifluoroacetic acid or formic acid) leads to the compounds of the general formula 12. Treatment with sulfonyl chlorides in presence of a base (e.g. N,N-dimethylaminopyridine or pyridine) yields compound 13. Deprotection of the protecting group L² (for L²=ethylcarbamate e.g. ethanolic potassium hydroxide) will lead to the free amine of the general formula 14. Reductive amination using the corresponding ketones or aldehydes in presence of...
a reduction reagent (e.g. sodium cyanoborohydride and glacial acetic acid) or amide formation followed by subsequent reduction yields the corresponding higher alkylated amines of the general formula 15. Reduction of the ethylcarbamate (L) of compound 13 (e.g. using lithium aluminum hydride) leads directly to compounds of the general formula 15 with R^4\textsuperscript{a}=methyl and R^4\textsuperscript{b}=hydrogen or vice versa.

In scheme 3, the variables R\textsuperscript{1}, W, A\textsuperscript{1}, R\textsuperscript{2}, R\textsuperscript{3}, R\textsuperscript{4\textsuperscript{a}}, R\textsuperscript{4\textsuperscript{b}}, R\textsuperscript{5}, R\textsuperscript{6}, X\textsuperscript{2}, X\textsuperscript{3}, n\textsubscript{1} and n\textsubscript{2} are as defined herein, and L\textsuperscript{1} and L\textsuperscript{2} are suitable protecting groups (e.g. L\textsuperscript{1}=Me, and L\textsuperscript{2}=COOEt).

The process depicted in scheme 4 is useful for obtaining aminochromanes, wherein X\textsuperscript{1} is -CH\textsuperscript{2}-, Y is -NR\textsuperscript{8}-, and Q is -S(0)\textsubscript{2}-.  

Scheme 4:

Triflates of the general formula 10 can be reacted with the corresponding alkyl iodides in the presence of zinc and palladium (e.g. zinc, TMSCl, 1,2-dibromoethane, Pd(dbda\textsubscript{2}, and dpf) to undergo a Negishi-coupling (Austr. J. Chem. 2004, 57, 107) and lead to compounds of the general formula 16. Alternatively, a Suzuki-coupling of the triflates 10 with the corresponding boron reagents (boronic acid, ester or trifluoroborates) in presence of a palladium source (e.g. palladium dibenzylidine acetone), a ligand (e.g. 2-dicyclohexyl-phosphino-2',6'-disopropoxybiphenyl) and a base (e.g. cesium carbonate) leads to the compounds of the general formula 16. Deprotection of the Boc-group in presence of an acid (e.g. trifluoroacetic acid or formic acid) leads to the compounds of the general formula 17. Treatment with sulfonyl chlorides in presence of a base (e.g. N,N-
dimethylaminopyridine or pyridine) yields compound 18. Deprotection of the protecting group L (for L = ethylcarbamate e.g. ethanolic potassium hydroxide) will lead to the free amine of the general formula 19. Reductive amination using the corresponding ketones or aldehydes in presence of a reduction reagent (e.g. sodiumcyanoborohydride and glacial acetic acid) or amide formation followed by subsequent reduction yields the corresponding higher alkylated amines of the general formula 20. Reduction of the ethylcarbamate (L) of compound 18 (e.g. using lithium aluminum hydride) leads directly to compounds of the general formula 20 with R^3=methyl and R^4=hydrogen or vice versa.

In scheme 4, the variables R^1, W, A^1, R^2, R^3, R^4, R^5, R^6, R^8, X^2, X^3, nl and n2 are as defined herein, and L is a suitable protecting groups (e.g. L = COOEt).

The compounds of the formula (I) are capable of inhibiting the activity of glycine transporter, in particular glycine transporter 1 (GlyT1).

The utility of the compounds in accordance with the present invention as inhibiting the glycine transporter activity, in particular GlyT1 activity, may be demonstrated by methodology known in the art. For instance, human GlyT1 c expressing recombinant hGlyTlc_5_CHO cells can be used for measuring glycine uptake and its inhibition (IC_50) by a compound of formula (I).

Amongst the compounds of the formula (I) those are preferred which achieve effective inhibition at low concentrations. In particular, compounds of the formula (I) are preferred which inhibit glycine transporter 1 (GlyT1) at a level of IC_50 < 1 μM, more preferably at a level of IC_50 < 0.5 μM, particularly preferably at a level of IC_50 < 0.2 μM and most preferably at a level of IC_50 < 0.1 μM.

Compounds of formula (I) combine high affinity with high metabolic stability.

The metabolic stability of a compound can be measured for example by incubating a solution of this compound with liver microsomes from particular species (for example rat, dog or human) and determining the half-life of the compound under these conditions (RS Obach, Curr Opin Drug Discov Devel. 2001, 4, 36-44). It is possible in this connection to conclude from an observed longer half-life that the metabolic stability of the compound is improved. The stability in the presence of human liver microsomes is of particular interest because it makes it possible to predict the metabolic degradation of the compound in the human liver. Compounds with increased metabolic stability (measured in the liver microsome test) are therefore probably also degraded more slowly in the liver. The slower metabolic degradation in the liver may lead to higher and/or longer-lasting concentrations (active levels) of the compound in the body, so that the elimination half-life of the compounds of the invention is increased. Increased and/or longer-lasting active levels may lead to a better activity of the compound in therapeutic treatment. In addition, an improved metabolic stability may lead to an increased bioavailability after oral administration, because the compound is subject, after absorption in the intestine, to less metabolic degradation in the liver (so-called first pass
effect). An increased oral bioavailability may, owing to an increased concentration (active level) of the compound, lead to a better activity of the compound after oral administration.

Amongst the compounds of the formula (I) those are particularly preferred which display good to moderate metabolic stability towards human liver microsomes. In particular, compounds of the formula (I) are preferred which display a microsomal clearance at a level of mClint,u < 500 L/h/kg, more preferably at a level of mClint,u < 100L/h/kg, particularly preferably at a level of mClint,u < 50L/h/kg, and most preferably at a level of mClint,u < 5 L/h/kg.

Further, compounds of formula (I) exhibit favorable efflux properties which may lead to enhanced oral bioavailability and/or increased brain availability. According to a particular embodiment, compounds of the invention combine high affinity and high metabolic stability with favorable efflux properties.

The efflux properties of a compound can be measured in well-known assays (e.g. Caco-2, MDCK assay).

The compounds of the formula (I) according to the present invention are thus useful as pharmaceuticals.

The present invention therefore also relates to pharmaceutical compositions which comprise an inert carrier and a compound of the formula (I).

The present invention also relates to the use of the compounds of the formula (I) in the manufacture of a medicament for inhibiting the glycine transporter GlyT1, and to corresponding methods of inhibiting the glycine transporter GlyT1.

The NMDA receptor is central to a wide range of CNS processes, and its role in a variety of diseases in humans or other species has been described. GlyT1 inhibitors slow the removal of glycine from the synapse, causing the level of synaptic glycine to rise. This in turn increases the occupancy of the glycine binding site on the NMDA receptor, which increases activation of the NMDA receptor following glutamate release from the presynaptic terminal. Glycine transport inhibitors and in particular inhibitors of the glycine transporter GlyT1 are thus known to be useful in treating a variety of neurologic and psychiatric disorders. Further, glycine A receptors play a role in a variety of diseases in humans or other species. Increasing extracellular glycine concentrations by inhibiting glycine transport may enhance the activity of glycine A receptors. Glycine transport inhibitors and in particular inhibitors of the glycine transporter GlyT1 are thus useful in treating a variety of neurologic and psychiatric disorders.

The present invention thus further relates to the use of the compounds of the formula (I) for the manufacture of a medicament for treating a neurologic or psychiatric disorder, and to corresponding methods of treating said disorders.
According to a particular embodiment, the disorder is associated with glycinergic or glutamatergic neurotransmission dysfunction.
nary incontinence; neuronal damage including ocular damage, retinopathy or macular degeneration of the eye, tinnitus, hearing impairment and loss, and brain edema; emesis; and sleep disorders including insomnia and narcolepsy.

According to a further particular embodiment, the disorder is pain, in particular chronic pain and especially neuropathic pain.

Pain can be classified as acute and chronic pain. Acute pain and chronic pain differ in their etiology, pathophysiology, diagnosis and treatment.

Acute pain, which occurs following tissue injury, is self-limiting, serves as an alert to ongoing tissue damage and following tissue repair it will usually subside. There are minimal psychological symptoms associated with acute pain apart from mild anxiety. Acute pain is nociceptive in nature and occurs following chemical, mechanical and thermal stimulation of A-delta and C-polymodal pain receptors.

Chronic pain, on the other hand, serves no protective biological function. Rather than being the symptom of tissue damage it is a disease in its own right. Chronic pain is unrelenting and not self-limiting and can persist for years, perhaps decades after the initial injury. Chronic pain can be refractory to multiple treatment regimes. Psychological symptoms associated with chronic pain include chronic anxiety, fear, depression, sleeplessness and impairment of social interaction. Chronic non-malignant pain is predominantly neuropathic in nature and involves damage to either the peripheral or central nervous systems.

Acute pain and chronic pain are caused by different neuro-physiological processes and therefore tend to respond to different types of treatments. Acute pain can be somatic or visceral in nature. Somatic pain tends to be a well localised, constant pain and is described as sharp, aching, throbbing or gnawing. Visceral pain, on the other hand, tends to be vague in distribution, paroxysmal in nature and is usually described as deep, aching, squeezing or colicky in nature. Examples of acute pain include post-operative pain, pain associated with trauma and the pain of arthritis. Acute pain usually responds to treatment with opioids or non-steroidal anti-inflammatory drugs.

Chronic pain, in contrast to acute pain, is described as burning, electric, tingling and shooting in nature. It can be continuous or paroxysmal in presentation. The hallmarks of chronic pain are chronic allodynia and hyperalgesia. Allodynia is pain resulting from a stimulus that normally does not elicit a painful response, such as a light touch. Hyperalgesia is an increased sensitivity to normally painful stimuli. Primary hyperalgesia occurs immediately within the area of the injury. Secondary hyperalgesia occurs in the undamaged area surrounding the injury. Examples of chronic pain include complex regional pain syndrome, pain arising from peripheral neuropathies, post-operative pain, chronic fatigue syndrome pain, tension-type headache, pain arising from mechanical nerve injury and severe pain associated with diseases such as cancer, metabolic disease, neuro-
tropic viral disease, neurotoxicity, inflammation, multiple sclerosis or any pain arising as a consequence of or associated with stress or depressive illness.

Although opioids are cheap and effective, serious and potentially life-threatening side effects occur with their use, most notably respiratory depression and muscle rigidity. In addition the doses of opioids which can be administered are limited by nausea, emesis, constipation, pruritis and urinary retention, often resulting in patients electing to receive sub-optimal pain control rather than suffer these distressing side-effects. Furthermore, these side-effects often result in patients requiring extended hospitalisation. Opioids are highly addictive and are scheduled drugs in many territories.

The compounds of formula (I) are particularly useful in the treatment of schizophrenia, bipolar disorder, depression including unipolar depression, seasonal depression and post-partum depression, premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PDD), learning disorders, pervasive developmental disorder including autistic disorder, attention deficit disorders including Attention-Deficit/Hyperactivity Disorder, tic disorders including Tourette's disorder, anxiety disorders including phobia and post traumatic stress disorder, cognitive disorders associated with dementia, AIDS dementia, Alzheimer's, Parkinson's, Huntington's disease, spasticity, myoclonus, muscle spasm, tinnitus and hearing impairment and loss are of particular importance.

Particular cognitive disorders are dementia, delirium, amnestic disorders and cognitive impairment including age-related cognitive decline.

Particular anxiety disorders are generalized anxiety disorder, obsessive-compulsive disorder and panic attack.

Particular schizophrenia or psychosis pathologies are paranoid, disorganized, catatonic or undifferentiated schizophrenia and substance-induced psychotic disorder.

Particular neurologic disorders that can be treated with the compounds of of the formula (I) include in particular a cognitive disorder such as dementia, cognitive impairment, attention deficit hyperactivity disorder.

Particular psychiatric disorders that can be treated with the compounds of of the formula (I) include in particular an anxiety disorder, a mood disorder such as depression or a bipolar disorder, schizophrenia, a psychotic disorder.

Within the context of the treatment, the use according to the invention of the compounds of the formula (I) involves a method. In this method, an effective quantity of one or more compounds or the formula (I), as a rule formulated in accordance with pharmaceutical and veterinary practice, is administered to the individual to be treated, preferably a mammal, in particular a human being. Whether such a treatment is indicated, and in which form it is to take place, depends on the individual case and is subject to medical assessment (diagnosis) which takes into consideration signs,
symptoms and/or malfunctions which are present, the risks of developing particular signs, symptoms and/or malfunctions, and other factors.

As a rule, the treatment is effected by means of single or repeated daily administration, where appropriate together, or alternating, with other drugs or drug-containing preparations.

The invention also relates to the manufacture of pharmaceutical compositions for treating an individual, preferably a mammal, in particular a human being. Thus, the compounds of the formula (I) are customarily administered in the form of pharmaceutical compositions which comprise an inert carrier (e.g. a pharmaceutically acceptable excipient) together with at least one compound according to the invention and, where appropriate, other drugs. These compositions can, for example, be administered orally, rectally, transdermally, subcutaneously, intravenously, intramuscularly or intranasally.

Examples of suitable pharmaceutical formulations are solid medicinal forms, such as powders, granules, tablets, in particular film tablets, lozenges, sachets, cachets, sugar-coated tablets, capsules, such as hard gelatin capsules and soft gelatin capsules, suppositories or vaginal medicinal forms, semisolid medicinal forms, such as ointments, creams, hydrogels, pastes or plasters, and also liquid medicinal forms, such as solutions, emulsions, in particular oil-in-water emulsions, suspensions, for example lotions, injection preparations and infusion preparations, and eyedrops and eardrops. Implanted release devices can also be used for administering inhibitors according to the invention. In addition, it is also possible to use liposomes or microspheres.

When producing the compositions, the compounds according to the invention are optionally mixed or diluted with one or more carriers (excipients). Carriers (excipients) can be solid, semisolid or liquid materials which serve as vehicles, carriers or medium for the active compound.

Suitable carriers (excipients) are listed in the specialist medicinal monographs. In addition, the formulations can comprise pharmaceutically acceptable auxiliary substances, such as wetting agents; emulsifying and suspending agents; preservatives; antioxidants; antiirritants; chelating agents; coating auxiliaries; emulsion stabilizers; film formers; gel formers; odor masking agents; taste corrigents; resin; hydrocolloids; solvents; solubilizers; neutralizing agents; diffusion accelerators; pigments; quaternary ammonium compounds; refatting and overfatting agents; raw materials for ointments, creams or oils; silicone derivatives; spreading auxiliaries; stabilizers; sterilants; suppository bases; tablet auxiliaries, such as binders, fillers, glidants, disintegrants or coatings; propellants; drying agents; opacifiers; thickeners; waxes; plasticizers and white mineral oils. A formulation in this regard is based on specialist knowledge as described, for example, in Fiedler, H.P., Lexikon der Hilfsstoffe fur Pharmazie, Kosmetik und angrenzende Gebiete [Encyclopedia of auxiliary substances for pharmacy, cosmetics and related fields], 4th edition, Aulendorf: ECV-Editio-Cantor-Verlag, 1996.

The compounds of formula (I) may also be suitable for combination with other therapeutic agents.
Thus, the present invention also provides:

i) a combination comprising a compound of formula (I) with one or more further therapeutic agents;

ii) a pharmaceutical composition comprising a combination product as defined in i) above and at least one carrier, diluent or excipient;

iii) the use of a combination as defined in i) above in the manufacture of a medicament for treating or preventing a disorder, disease or condition as defined herein;

iv) a combination as defined in i) above for use in treating or preventing a disorder, disease or condition as defined herein;

v) a kit-of-parts for use in the treatment of a disorder, disease or condition as defined herein, comprising a first dosage form comprising a compound of formula (I) and one or more further dosage forms each comprising one or more further therapeutic agents for simultaneous therapeutic administration,

vi) a combination as defined in i) above for use in therapy;

vii) a method of treatment or prevention of a disorder, disease or condition as defined herein comprising administering an effective amount of a combination as defined in i) above;

viii) a combination as defined in i) above for treating or preventing a disorder, disease or condition as defined herein.

The combination therapies of the invention may be administered adjunctively. By adjunctive administration is meant the coterminous or overlapping administration of each of the components in the form of separate pharmaceutical compositions or devices. This regime of therapeutic administration of two or more therapeutic agents is referred to generally by those skilled in the art and herein as adjunctive therapeutic administration; it is also known as add-on therapeutic administration. Any and all treatment regimes in which a patient receives separate but coterminous or overlapping therapeutic administration of the compounds of formula (I) and at least one further therapeutic agent are within the scope of the current invention. In one embodiment of adjunctive therapeutic administration as described herein, a patient is typically stabilised on a therapeutic administration of one or more of the components for a period of time and then receives administration of another component.

The combination therapies of the invention may also be administered simultaneously. By simultaneous administration is meant a treatment regime wherein the individual components are administered together, either in the form of a single pharmaceutical composition or device comprising or containing both components, or as separate compositions or devices, each comprising one of the components, administered simultaneously. Such combinations of the separate individual components for simultaneous combination may be provided in the form of a kit-of-parts.

In a further aspect, the invention provides a method of treatment of a psychotic disorder by adjunctive therapeutic administration of compounds of formula (I) to a patient receiving therapeutic administration of at least one antipsychotic agent. In a further aspect, the invention provides the use
of compounds of formula (I) in the manufacture of a medicament for adjunctive therapeutic administration for the treatment of a psychotic disorder in a patient receiving therapeutic administration of at least one antipsychotic agent. The invention further provides compounds of formula (I) for use for adjunctive therapeutic administration for the treatment of a psychotic disorder in a patient receiving therapeutic administration of at least one antipsychotic agent.

In a further aspect, the invention provides a method of treatment of a psychotic disorder by adjunctive therapeutic administration of at least one antipsychotic agent to a patient receiving therapeutic administration of compounds of formula (I). In a further aspect, the invention provides the use of at least one antipsychotic agent in the manufacture of a medicament for adjunctive therapeutic administration for the treatment of a psychotic disorder in a patient receiving therapeutic administration of compounds of formula (I). The invention further provides at least one antipsychotic agent for adjunctive therapeutic administration for the treatment of a psychotic disorder in a patient receiving therapeutic administration of compounds of formula (I).

In a further aspect, the invention provides a method of treatment of a psychotic disorder by simultaneous therapeutic administration of compounds of formula (I) in combination with at least one antipsychotic agent. The invention further provides the use of a combination of compounds of formula (I) and at least one antipsychotic agent in the manufacture of a medicament for simultaneous therapeutic administration in the treatment of a psychotic disorder. The invention further provides a combination of compounds of formula (I) and at least one antipsychotic agent for simultaneous therapeutic administration in the treatment of a psychotic disorder. The invention further provides the use of compounds of formula (I) in the manufacture of a medicament for simultaneous therapeutic administration with at least one antipsychotic agent in the treatment of a psychotic disorder. The invention further provides compounds of formula (I) for use for simultaneous therapeutic administration with at least one antipsychotic agent in the treatment of a psychotic disorder. The invention further provides the use of at least one antipsychotic agent in the manufacture of a medicament for simultaneous therapeutic administration with compounds of formula (I) in the treatment of a psychotic disorder. The invention further provides at least one antipsychotic agent for simultaneous therapeutic administration with compounds of formula (I) in the treatment of a psychotic disorder.

In further aspects, the invention provides a method of treatment of a psychotic disorder by simultaneous therapeutic administration of a pharmaceutical composition comprising compounds of formula (I) and at least one mood stabilising or antimanic agent, a pharmaceutical composition comprising compounds of formula (I) and at least one mood stabilising or antimanic agent, the use of a pharmaceutical composition comprising compounds of formula (I) and at least one mood stabilising or antimanic agent in the manufacture of a medicament for the treatment of a psychotic disorder, and a pharmaceutical composition comprising compounds of formula (I) and at least one mood stabilising or antimanic agent for use in the treatment of a psychotic disorder.
Antipsychotic agents include both typical and atypical antipsychotic drugs. Examples of antipsychotic drugs that are useful in the present invention include, but are not limited to: butyrophenones, such as haloperidol, pimozide, and droperidol; phenothiazines, such as chlorpromazine, thioridazine, mesoridazine, trifluoperazine, perphenazine, fluphenazine, thiflupromazine, prochlorperazine, and acetophenazine; thioxanthenes, such as thiothixene and chlorprothixene; thienobenzodiazepines; dibenzodiazepines; benzisoxazoles; dibenzothiazepines; imidazolidinones; benzo- thiazolyl-piperazines; triazine such as lamotrigine; dibenzoazepines, such as loxapine; dihydroidolones, such as molindone; aripiprazole; and derivatives thereof that have antipsychotic activity.

Examples of tradenames and suppliers of selected antipsychotic drugs are as follows: clozapine (available under the tradename CLOZARIL®, from Mylan, Zenith Goldline, UDL, Novartis); olanzapine (available under the tradename ZYPREX®, from Lilly); ziprasidone (available under the tradename GEODON®, from Pfizer); risperidone (available under the tradename RISPERDAL®, from Janssen); quetiapine fumarate (available under the tradename SEROQUEL®, from AstraZeneca); haloperidol (available under the tradename HALDOL®, from Ortho-McNeil); chlorpromazine (available under the tradename THORAZINE®, from SmithKline Beecham (GSK)); fluphenazine (available under the tradename PROLIXIN®, from Apothecon, Copley, Schering, Teva, and American Pharmaceutical Partners, Pasadena); thiothixene (available under the tradename NAVANE®, from Pfizer); trifluoperazine (10-[3-(4-methyl-1-piperazinyl)propyl]-2-(trifluoromethyl)phenothiazine dihydrochloride, available under the tradename STELAZINE®, from Smith Klein Beckman); perphenazine (available under the tradename TRILAFON®, from Schering); thioridazine (available under the tradename MELLARIL®, from Novartis, Roxane, HiTech, Teva, and Alpharma); molindone (available under the tradename MOBAN®, from Endo); and loxapine (available under the tradename LOXITANE(D from Watson). Furthermore, benperidol (Gliainosinom®), perazine (Taxilan®) or melperone (Eunerpan®) may be used. Other antipsychotic drugs include promazine (available under the tradename SPARINE®, triflurpromazine (available under the tradename VESPRI N®), chlorprothixene (available under the tradename TARACTAN®), droperidol (available under the tradename INAPSINE®), acetophenazine (available under the tradename TINDAL®), prochlorperazine (available under the tradename COMPAZTNE®), methotrimeprazine (available under the tradename NOZTAN®), pipotiazine (available under the tradename PIPOTRIL®), ziprasidone, and hopenilone.

In a further aspect, the invention provides a method of treatment of a neurodegenerative disorder such as Alzheimer Disease by adjunctive therapeutic administration of compounds of formula (I) to a patient receiving therapeutic administration of at least one agent suitable for the treatment of a neurodegenerative disorder such as Alzheimer Disease. In a further aspect, the invention provides the use of compounds of formula (I) in the manufacture of a medicament for adjunctive therapeutic administration for the treatment of a neurodegenerative disorder such as Alzheimer Disease in a patient receiving therapeutic administration of at least one agent suitable for the treatment of a neurodegenerative disorder such as Alzheimer Disease. The invention further provides compounds of formula (I) for use for adjunctive therapeutic administration for the treatment of a neurodegenera-
tive disorder such as Alzheimer Disease in a patient receiving therapeutic administration of at least one agent suitable for the treatment of a neurodegenerative disorder such as Alzheimer Disease.

In a further aspect, the invention provides a method of treatment of a neurodegenerative disorder such as Alzheimer Disease by adjunctive therapeutic administration of at least one agent suitable for the treatment of a neurodegenerative disorder such as Alzheimer Disease to a patient receiving therapeutic administration of compounds of formula (I). In a further aspect, the invention provides the use of at least one agent suitable for the treatment of a neurodegenerative disorder such as Alzheimer Disease in the manufacture of a medicament for adjunctive therapeutic administration for the treatment of a neurodegenerative disorder such as Alzheimer Disease in a patient receiving therapeutic administration of compounds of formula (I). The invention further provides at least one agent suitable for the treatment of a neurodegenerative disorder such as Alzheimer Disease for adjunctive therapeutic administration for the treatment of a neurodegenerative disorder such as Alzheimer Disease in a patient receiving therapeutic administration of compounds of formula (I).

In a further aspect, the invention provides a method of treatment of a neurodegenerative disorder such as Alzheimer Disease by simultaneous therapeutic administration of compounds of formula (I) in combination with at least one agent suitable for the treatment of a neurodegenerative disorder such as Alzheimer Disease. The invention further provides the use of a combination of compounds of formula (I) and at least one agent suitable for the treatment of a neurodegenerative disorder such as Alzheimer Disease in the manufacture of a medicament for simultaneous therapeutic administration in the treatment of a neurodegenerative disorder such as Alzheimer Disease. The invention further provides a combination of compounds of formula (I) and at least one agent suitable for the treatment of a neurodegenerative disorder such as Alzheimer Disease in the treatment of a neurodegenerative disorder such as Alzheimer Disease. The invention further provides compounds of formula (I) for use for simultaneous therapeutic administration with at least one agent suitable for the treatment of a neurodegenerative disorder such as Alzheimer Disease in the treatment of a neurodegenerative disorder such as Alzheimer Disease. The invention further provides the use of at least one agent suitable for the treatment of a neurodegenerative disorder such as Alzheimer Disease in the manufacture of a medicament for simultaneous therapeutic administration with compounds of formula (I) in the treatment of a neurodegenerative disorder such as Alzheimer Disease. The invention further provides at least one agent suitable for the treatment of a neurodegenerative disorder such as Alzheimer Disease for simultaneous therapeutic administration with compounds of formula (I) in the treatment of a neurodegenerative disorder such as Alzheimer Disease.

Examples of agents suitable for the treatment of a neurodegenerative disorder such as Alzheimer Disease that are useful in the present invention include, but are not limited to: cholinesterase inhibitors, agents targeting nicotinic or muscarinic acetylcholine receptors, NMDA receptors, amyloid
formation, mitochondrial dysfunctions, disease associated calpain activity, neuromflammation, tumor necrosis factor receptors, NF-kappaB, peroxisome proliferator activator receptor gamma, Apolipoprotein E variant 4 (ApoE4), disease-associated increase of the HPA axis, epileptic discharges, vascular dysfunction, vascular risk factors, and oxidative stress.

Suitable cholinesterase inhibitors which may be used in combination with the compounds of the inventions include for example tacrine, donepezil, galantamine and rivastigmine.

Suitable NMDA receptors targeting agents which may be used in combination with the compounds of the inventions include for example memantine.

Suitable agents affecting increased HPA axis activity which may be used in combination with the compounds of the inventions include for example CRF1 antagonists or V1b antagonists.

In a further aspect therefore, the invention provides a method of treatment of pain by adjunctive therapeutic administration of compounds of formula (I) to a patient receiving therapeutic administration of at least one agent suitable for the treatment of pain. In a further aspect, the invention provides the use of compounds of formula (I) in the manufacture of a medicament for adjunctive therapeutic administration for the treatment of pain in a patient receiving therapeutic administration of at least one agent suitable for the treatment of pain. The invention further provides compounds of formula (I) for use for adjunctive therapeutic administration for the treatment of pain in a patient receiving therapeutic administration of at least one agent suitable for the treatment of pain.

In a further aspect, the invention provides a method of treatment of pain by adjunctive therapeutic administration of at least one agent suitable for the treatment of pain to a patient receiving therapeutic administration of compounds of formula (I). In a further aspect, the invention provides the use of at least one agent suitable for the treatment of pain in the manufacture of a medicament for adjunctive therapeutic administration for the treatment of pain in a patient receiving therapeutic administration of compounds of formula (I). The invention further provides at least one agent suitable for the treatment of pain for adjunctive therapeutic administration for the treatment of pain in a patient receiving therapeutic administration of compounds of formula (I).

In a further aspect, the invention provides a method of treatment of pain by simultaneous therapeutic administration of compounds of formula (I) in combination with at least one agent suitable for the treatment of pain. The invention further provides the use of a combination of compounds of formula (I) and at least one agent suitable for the treatment of pain in the manufacture of a medicament for simultaneous therapeutic administration in the treatment of pain. The invention further provides a combination of compounds of formula (I) and at least one agent suitable for the treatment of pain for simultaneous therapeutic administration in the treatment of pain. The invention further provides the use of compounds of formula (I) in the manufacture of a medicament for simultaneous therapeutic administration with at least one agent suitable for the treatment of pain in the treatment of pain. The invention further provides compounds of formula (I) for use for simultane-
ous therapeutic administration with at least one agent suitable for the treatment of pain in the treatment of pain. The invention further provides the use of at least one agent suitable for the treatment of pain in the manufacture of a medicament for simultaneous therapeutic administration with compounds of formula (I) in the treatment of pain. The invention further provides at least one agent suitable for the treatment of pain for simultaneous therapeutic administration with compounds of formula (I) in the treatment of pain.

Examples of agents suitable for the treatment of pain that are useful in the present invention include, but are not limited to: NSAIDs (Nonsteroidal Antiinflammatory Drugs), anticonvulsant drugs such as carbamazepine and gabapentin, sodium channel blockers, antidepressant drugs, cannabinoids and local anaesthetics.

Suitable agents used in combination with the compounds of the inventions include for example celecoxib, etoricoxib, lumiracoxib, paracetamol, tramadol, methadone, venlafaxine, imipramine, duloxetine, bupropion, gabapentin, pregabalin, lamotrigine, fentanyl, parecoxib, nefopam, remifentanil, pethidine, diclofenac, rofecoxib, nalbuphine, sufentanil, pethidine, diamorphine and butorphanol.

It will be appreciated by those skilled in the art that the compounds according to the invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, antidepressant agents such as 5HT3 antagonists, serotonin agonists, NK-1 antagonists, selective serotonin reuptake inhibitors (SSRI), noradrenaline re-uptake inhibitors (SNRI), tricyclic antidepressants, dopaminergic antidepressants, H3 antagonists, 5HT1A antagonists, 5HT1 B antagonists, 5HT1 D antagonists, D1 agonists, M1 agonists and/or anticonvulsant agents, as well as cognitive enhancers.

Suitable 5HT3 antagonists which may be used in combination of the compounds of the inventions include for example ondansetron, granisetron, metoclopramide.

Suitable serotonin agonists which may be used in combination with the compounds of the invention include sumatriptan, rauwolscine, yohimbine, metoclopramide.

Suitable SSRIs which may be used in combination with the compounds of the invention include fluoxetine, citalopram, femailetine, fluvoxamine, paroxetine, indalpine, sertraline, zimeldine.

Suitable SNRIs which may be used in combination with the compounds of the invention include venlafaxine and reboxetine.

Suitable tricyclic antidepressants which may be used in combination with a compound of the invention include imipramine, amitriptiline, chlorimipramine and nortriptiline.
Suitable dopaminergic antidepressants which may be used in combination with a compound of the invention include bupropion and amineptine.

Suitable anticonvulsant agents which may be used in combination of the compounds of the invention include for example divalproex, carbamazepine and diazepam.

The following examples serve to explain the invention without limiting it.

The compounds were characterized by mass spectrometry, generally recorded via HPLC-MS in a fast gradient on C18-material (electrospray-ionisation (ESI) mode).

Preparation Examples

Example 1: N-[1-[3-(azetidin-1-yl)-4-benzyl-chroman-6-yl] azetidin-3-yl]-1-methyl-imidazole-4-sulfonamide

\[
\text{ESI-MS} \ [\text{M+H}^+] = 194 \quad \text{Calculated for C}_{10}\text{H}_{11}\text{NO}_3 = 193.
\]

1.1 6-Methoxychroman-4-one oxime

5.2 g (29.2 mmol) of 6-methoxychroman-4-one were dissolved in ethanol and 2.53 g (36.5 mmol) hydroxylamine hydrochloride and 2.99 g (36.5 mmol) sodium acetate dissolved in 10 ml of water were added. The mixture was stirred at 65 °C for 1.5 hours. The mixture was allowed to cool to room temperature and concentrated. The residue was dissolved in methyl-tert-butylether. The organic phase was washed with water, dried over MgSO$_4$ and concentrated to give 5.6 g (29.4 mmol, quant.) of crude product, which was directly used in the next step.

ESI-MS [M+H$^+$] = 194 \quad \text{Calculated for C}_{10}\text{H}_{11}\text{NO}_3 = 193.
1.2 6-Methoxychroman-4-one O-tosyl oxime

5.68 g (29.4 mmol) of 6-methoxychroman-4-one oxime were dissolved under argon atmosphere in 30 ml of dry pyridine. At 0°C 6.05 g (31.8 mmol) of 4-methylbenzene-1-sulfonyl chloride were added in small portions over 40 min. The mixture was stirred at 0°C for an additional hour and then warmed to room temperature and stirred overnight. The mixture was poured into 260 ml ice water, stirred, and the suspension was filtered. The solid residue was washed with a small amount of cold water (2x) and cold ethanol (1x), and dried to yield 8.96 g (25.8 mmol, 88%) of desired product.

ESI-MS [M+H+] = 348  Calculated for C_{17}H_{17}NO_{5}S = 347.

1.3 3-Amino-6-methoxychroman-4-one hydrochloride

To a solution of sodium ethoxide (10.5 ml, 28.1 mmol, 21% in ethanol) under nitrogen atmosphere at 0°C was added a suspension of 8.96 g (25.8 mmol) of (Z)-6-methoxychroman-4-one O-tosyl oxime in toluene. The mixture was stirred over night and slowly warmed to room temperature. The suspension was filtered and rinsed with ether. 95 ml (190 mmol) of an aqueous solution of hydrogen chloride (2 N) was added to the filtrate and stirred at room temperature for 2 h. The suspension was diluted with 150 ml of water and phases were separated. The organic phase was extracted with aqueous hydrogen chloride solution (2x, 20-30 ml, 1 N) and water (1x, 30 ml). The combined aqueous layers were washed with ether (1x). The aqueous phase was stirred with a small amount of activated charcoal, filtered, and concentrated to a 1/5 of its volume until a crystalline precipitation was observed. The mixture was cooled to 0°C and the crystalline material was filtered off, washed with a small amount of cold ethanol, and dried in vacuo. The filtrate was also concentrated in vacuo. 3.67 g (15.98 mmol, 62%) of combined crude desired product was obtained.

ESI-MS [M+H+] = 194  Calculated for C_{10}H_{11}NO_{3} = 193.

1.4 Ethyl 6-methoxy-4-oxochroman-3-ylcarbamate
2.82 g (12.3 mmol) of 6-methoxy-4-oxochroman-3-aminium chloride were dissolved in tetrahydrofuran under nitrogen atmosphere and cooled to 0 °C with an ice bath. Diisopropylethylamine and ethyl carbononochloridate were added. The mixture was allowed to warm to room temperature and stirred for 30 min. The mixture was diluted with ethyl acetate and washed with saturated ammonium chloride solution (2x) and water (1x). The organic phase was washed, dried over MgSO₄, and concentrated in vacuo to give 3.5 g (13.2 mmol, quant.) of crude material.

ESI-MS [M+H⁺] = 265  Calculated for C₁₃H₁₅N₀₅ = 266.

1.5 Ethyl 4-benzyl-4-hydroxy-6-methoxychroman-3-ylcarbamate

26.4 ml (52.8 mmol) of benzylmagnesium chloride under nitrogen atmosphere were cooled to 0 °C with an ice bath and 3.5 g (13.2 mmol) ethyl 6-methoxy-4-oxochroman-3-ylcarbamate dissolved in 100 ml dry THF were slowly added. The mixture was stirred at 0 °C for 1 h. The cooling bath was removed and saturated ammonium chloride solution was added. Water was added until a clear solution was obtained. The phases were separated and the organic phase was washed with saturated ammonium chloride solution, dried over MgSO₄, and concentrated in vacuo to give 6.87 g (9.1 mmol, quant.) of crude material.

ESI-MS [M+Na⁺] = 380  Calculated for C₂₀H₂₃NO₅ = 357.

1.6 Ethyl 4-benzylidene-6-methoxychroman-3-ylcarbamate

6.87 g (12.5 mmol) of ethyl 4-benzyl-4-hydroxy-6-methoxychroman-3-ylcarbamate were added to 80 ml of half concentrated aqueous hydrochloric acid and stirred at 100 °C for 2.5 h. The mixture was cooled to 0 °C and diluted with water. Sodium hydroxide (50 % aqueous solution) was carefully added until pH > 10. The aqueous phase was extracted with EtOAc (2x). The combined organic
phases were washed with water and brine, dried over MgSO₄ and the solvent was evaporated to give 5.7 g of crude material. The crude material was purified by flash chromatography to yield 3.1 g (9.1 mmol, 73 %) of the desired product.

ESI-MS [M+H⁺] = 339 Calculated for C₂₀H₂₁NO₄ = 340.

1.7 Ethyl 4-benzyl-6-methoxychroman-3-ylcarbamate

\[
\text{H} \quad \text{O} \quad \text{N} \quad \text{O} \quad \text{O}
\]

3.1 g (9.1 mmol) of ethyl 4-benzylidene-6-methoxychroman-3-ylcarbamate were dissolved in 80 ml of EtOH and 910 mg (0.9 mmol) of Pd/C were added. Then, 5.8 g (91 mmol) of ammonium formiate dissolved in 20 ml of water were added and the mixture was warmed to 70 °C and stirred for 1.5 h. The mixture was cooled to room temperature. The catalyst was filtered off and washed with EtOH/water. The filtrate was concentrated in vacuo to remove EtOH. The aqueous concentrate was extracted with ethyl acetate (2x). The combined organic phases were dried over MgSO₄ and the solvent was evaporated to yield 3.2 g (9.3 mmol, quant.) of the crude product (cis:trans ~ 7:1). The cis-isomer can be enriched (-26: 1) by crystallization from hot heptane.

ESI-MS [M+H⁺] = 342 Calculated for C₂₀H₂₃NO₄ = 341.

1.8 Ethyl 4-benzyl-6-hydroxychroman-3-ylcarbamate

\[
\text{H} \quad \text{O} \quad \text{N} \quad \text{O} \quad \text{O}
\]

3.19 g (9.3 mmol) of ethyl 4-benzyl-6-methoxychroman-3-ylcarbamate under nitrogen atmosphere were dissolved in 90 ml of methylene dichloride. At 0°C 28.0 ml (28.0 mmol, 1 M in methylene dichloride) of boron tribromide were added. The reaction mixture was stirred at 0 °C for 2 hours. At 0 °C saturated sodium hydrogencarbonate solution was added to the reaction mixture. The phases were separated and the aqueous phase was extracted with methylene dichloride. The combined organic layers were washed with brine, dried over MgSO₄ and the solvent was evaporated to yield 3.0 g (9.2 mmol, 99%) of the crude product.

ESI-MS [M+H⁺] = 328 Calculated for C₁₉H₂₁NO₄ = 327.

1.9 Cis-3-Amino-4-benzylchroman-6-ol and trans-3-Amino-4-benzylchroman-6-ol
2.3 g (7.0 mmol) of ethyl 4-benzyl-6-hydroxychroman-3-ylcarbamate were dissolved in ethanolic KOH 20% and stirred at 70°C over night. The solvent was evaporated, the residue partitioned between ethylacetate and water. The organic layer was washed twice with water and the combined water layer extracted another 2 times with ethyl acetate. The combined ethyl acetate extract was dried over MgSO₄, filtrated and evaporated. The crude material was purified by flash chromatography to yield 1.11 g (4.34 mmol, 62%) of cis-Isomer and 0.25 g (0.97 mmol, 14%) of the trans-Isomer.

Cis-Isomer: ESI-MS [M+H⁺] = 256 Calculated for C₁₆H₁₇NO₂ = 255.

Trans-Isomer: ESI-MS [M+H⁺] = 256 Calculated for C₁₆H₁₇NO₂ = 255.

1.10 Cis-3-(Azetidin-1-yl)-4-benzylchroman-6-ol

0.9 g (3.57 mmol) of cis-3-amino-4-benzylchroman-6-ol, 0.36 mL (3.55 mmol) 1,3-dibromopropane and 1.9 mL (10.88 mmol) N-ethyl-N-isopropylpropan-2-amine were combined with 18 mL acetonitrile and stirred at 130°C in the microwave (CEM) for 3 hours. Additional 75 μL 1,3-dibromopropane and 0.5 mL N-ethyl-N-isopropylpropan-2-amine were added to the reaction mixture (brown solution) and stirred at 130°C in the microwave (CEM) for an additional 1 hour. The reaction mixture was evaporated and the obtained residue partitioned between water and ethyl acetate. The organic phase was washed with water and brine and the combined aqueous phases extracted twice with ethyl acetate. Combined organic extracts were dried over MgSO₄, filtrated and evaporated to dryness to yield 1 g of crude material. The material was purified by flash chromatography to yield 0.6 g (2.01 mmol, 56%) of desired product.

ESI-MS [M+H⁺] = 296 Calculated for C₁₉H₂₁N₂O₂ = 295.

1.11 Cis-3-(Azetidin-1-yl)-4-benzylchroman-6-yl trifluoromethanesulfonate
0.6 g (2.00 mmol) of cis-3-(Azetidin-1-yl)-4-benzylchroman-6-ol were dissolved in methylene chloride under nitrogen, 0.5 mL (6.18 mmol) pyridine were added and cooled with an ice bath to 0 °C. 2.2 mL (2.20 mmol) trifluoromethanesulfonic anhydride were added and the reaction mixture stirred under cooling for 1 hour. The reaction mixture was quenched with aqueous bicarbonate solution, and the aqueous phase separated and extracted with methylene chloride once. The combined organic layers were washed with water (2x) and brine (1x), dried over MgSO₄, filtrated and evaporated to dryness to yield 0.8 g of crude material.

ESI-MS [M+H⁺] = 427  Calculated for C₂₀H₂₀F₃NO₄S = 428.

1.12 Cis-tert-Butyl (1-(3-(azetidin-1-yl)-4-benzylchroman-6-yl)azetidin-3-yl)carbamate

0.2 g (0.36 mmol) of cis-3-(azetidin-1-yl)-4-benzylchroman-6-yl trifluoromethanesulfonate were dissolved in toluene under nitrogen, 0.01 g (0.05 mmol) Pd(II) acetate, 0.05 g (0.11 mmol) dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine (x-Phos) and 0.35 g (1.07 mmol) cesium carbonate were added to this solution and the resulting mixture stirred at 115°C for 15 min. Then, 0.09 g (0.43 mmol) of 3-((tert-butoxycarbonyl)amino)azetidin-1-ium chloride was added and the reaction mixture stirred for 30 min. at 115 °C. The reaction mixture was allowed to cool at room temperature, the solvent evaporated, and the residue extracted between water and ethyl acetate. The organic phase was washed with brine, dried over MgSO₄, filtered and evaporated. The crude material was purified by flash chromatography to yield 0.15 g (0.33 mmol, 93 %).

ESI-MS [M+H⁺] = 450  Calculated for C₂₇H₃₅N₃O₃ = 449.

1.13 Cis-1-(3-(azetidin-1-yl)-4-benzylchroman-6-yl)azetidin-3-amine
0.15 g (0.33 mmol) of cis-tert-butyl (l-(3-(azetidin-l-yl)-4-benzylchroman-6-yl)azetidin-3-yl)carbamate were dissolved in methylene chloride, 0.25 mL (3.24 mmol) trifluoroacetic acid were added and the reaction mixture stirred at room temperature overnight. The solvents were evaporated. The residue was dissolved in water and washed twice with methyl-tert-butyl ether. The water layer was separated, aqueous sodium bicarbonate solution was added until pH 8 was reached, and extracted with methylene chloride (3x). The combined organic extracts were dried over MgSO$_4$ and concentrated to yield 0.10 g (0.29 mmol) of crude material.

ESI-MS [M+H$^+$] = 350  
Calculated for C$_{22}$H$_{27}$N$_3$O = 349.

1.14  Cis-N-(1-(3-(azetidin-1-yl)-4-benzylchroman-6-yl)azetidin-3-yl)-1-methyl-1H-imidazole-4-sulfonamide

0.05 g (0.14 mmol) of 1-(3-(azetidin-1-yl)-4-benzylchroman-6-yl)azetidin-3-amine were dissolved in methylene chloride, 0.05 g (0.37 mmol) N,N-dimethylpyridin-4-amine and 0.03 g (0.19 mmol) 1-methyl-1H-imidazole-4-sulfonyl chloride were added. The reaction mixture was stirred at room temperature for 30 min. The solvent was evaporated and the residue partitioned between ethyl acetate and water. The organic layer was washed twice with water, dried over MgSO$_4$, filtered and evaporated. The crude material was purified by flash chromatography to yield 0.06 g (0.11 mmol, 81%) of desired product.

ESI-MS [M+H$^+$] = 494  
Calculated for C$_{26}$H$_{31}$N$_5$O$_3$S = 349.

Example 2: Cis-N-(1-(3-(azetidin-1-yl)-4-benzylchroman-6-yl)azetidin-3-yl)ethanesulfonamide
Cis-N-(l-(3-(azetidin-1-yl)-4-benzylchroman-6-yl)azetidin-3-yl)ethanesulfonamide was prepared in analogy to example 1.

ESI-MS \([\text{M+H}^+] = 442\) Calculated for \(\text{C}_{24}\text{H}_{31}\text{N}_{3}\text{O}_{3}\text{S} = 441\).

Example 3: Cis-N-(l-(3-(azetidin-1-yl)-4-benzylchroman-6-yl)azetidin-3-yl)propane-1-sulfonamide

ESI-MS \([\text{M+H}^+] = 456\) Calculated for \(\text{C}_{25}\text{H}_{33}\text{N}_{3}\text{O}_{3}\text{S} = 455\).

Example 4: Cis-N-(l-(3-(azetidin-1-yl)-4-benzylchroman-6-yl)azetidin-3-yl)-l-cyclopropylmethanesulfonamide
Cis-N-(l-(3-(azetidin-1-yl)-4-benzylchroman-6-yl)azetidin-3-yl)-l-cyclopropylmethane-
sulfonamide was prepared in analogy to example 1.
ESI-MS [M+H⁺] = 468 Calculated for C₂₆H₃₃N₃O₃S = 467.

Example 5: Cis-N-(1-(3-(azetidin-1-yl)-4-benzylchroman-6-yl)azetidin-3-yl)-l-methyl-
1H-pyrazole-4-sulfonamide

![Chemical structure](image)

Cis-N-(1-(3-(azetidin-1-yl)-4-benzylchroman-6-yl)azetidin-3-yl)-l-methyl-
1H-pyrazole-4-sulfonamide was prepared in analogy to example 1.
ESI-MS [M+H⁺] = 494 Calculated for C₂₆H₃₁N₅O₃S = 493.

Example 6: Cis-N-(l-(3-(azetidin-1-yl)-4-benzylchroman-6-yl)azetidin-3-yl)-l-methyl-
1H,1,2,3-triazole-4-sulfonamide

![Chemical structure](image)

Cis-N-(l-(3-(azetidin-1-yl)-4-benzylchroman-6-yl)azetidin-3-yl)-l-methyl-
1H,1,2,3-triazole-4-sulfonamide was prepared in analogy to example 1.
ESI-MS [M+H⁺] = 495 Calculated for C₂₆H₃₀N₄O₃S = 494.

Example 7: Cis-N-(l-(3-(azetidin-1-yl)-4-benzyl-7-fluorochroman-6-yl)azetidin-3-yl)-l-ethyl-
1H,1,2,3-triazole-4-sulfonamide
Cis-N-(1-(3-(azetidin-1-yl)-4-benzyl-7-fluorochroman-6-yl)azetidin-3-yl)-1-ethyl-1H-1,2,3-triazole-4-sulfonamide was prepared in analogy to example 1.

ESI-MS [M+H⁺] = 527 Calculated for C₂₆H₂₇FN₃O₃S = 526.

Example 8: Cis-N-(1-(3-(azetidin-1-yl)-4-benzyl-7-fluorochroman-6-yl)azetidin-3-yl)-2-fluoropyridine-3-sulfonamide

Cis-N-(1-(3-(azetidin-1-yl)-4-benzyl-7-fluorochroman-6-yl)azetidin-3-yl)-2-fluoropyridine-3-sulfonamide was prepared in analogy to example 1.

ESI-MS [M+H⁺] = 527 Calculated for C₂₇H₂₈F₂N₄O₃S = 526.

Example 9: Cis-N-(1-(3-(azetidin-1-yl)-4-benzyl-7-fluorochroman-6-yl)azetidin-3-yl)pyridazine-3-sulfonamide

Cis-N-(1-(3-(azetidin-1-yl)-4-benzyl-7-fluorochroman-6-yl)azetidin-3-yl)pyridazine-3-sulfonamide was prepared in analogy to example 1.

ESI-MS [M+H⁺] = 510 Calculated for C₂₆H₂₇FN₃O₃S = 509.
Example 10: Cis-N-(1-(3-(azetidin-1-yl)-4-benzylchroman-6-yl)azetidin-3-yl)-2-fluoropyridine-3-sulfonamide

was prepared in analogy to example 1.

ESI-MS [M+H+] = 509 Calculated for C27H29FN4O3S = 508.

Example 11: Cis-N-(1-(4-benzyl-3-(methylamino)chroman-6-yl)azetidin-3-yl)propane-1-sulfonamide

11.1 Cis-4-benzyl-3-((ethoxycarbonyl)amino)chroman-6-yl trifluoromethanesulfonate

Cis-4-benzyl-3-((ethoxycarbonyl)amino)chroman-6-yl trifluoromethanesulfonate was prepared starting from cis-ethyl 4-benzyl-6-hydroxychroman-3-ylcarbamate (Example 1, 1.8).

4.9 g (14.97 mmol) of 4-benzyl-3-((ethoxycarbonyl)amino)chroman-6-yl trifluoromethanesulfonate were dissolved in methylene chloride under nitrogen atmosphere, 3.0 mL (37.4 mmol) pyridine were added and cooled to 0 °C with an ice bath. Then, 16.5 mL (16.5 mmol) trifluoromethanesulfonic anhydride (1 M in methylene chloride) were added and the reaction mixture stirred under cooling for 0.5 hour. The reaction mixture was quenched with aqueous ammonium chloride solution, the phases were separated, and the aqueous phase was extracted with methylene chloride once. The combined organic layers were washed with aqueous ammonium chloride solution and
brine, dried over MgSO$_4$, filtrated, and evaporated to dryness to yield 6.6 g (14.37 mmol, 96%) of crude product.

ESI-MS [M+H$^+$] = 460  Calculated for C$_{27}$H$_{35}$N$_3$O$_5$ = 459.11

11.2 Cis-tert-Butyl (1-((3-(azetidin-1-yl)-4-benzyl-3-((ethoxycarbonyl)amino)chroman-6-yl car bamate

![Chemical structure](image)

6.0 g (13.06 mmol) of cis-4-benzyl-3-((ethoxycarbonyl)amino)chroman-6-yl trifluoromethanesulfonate were dissolved in toluene under nitrogen atmosphere, 0.44 g (1.96 mmol) Pd(II) acetate, 1.87 g (3.92 mmol) dicyclohexyl(2',4',6'-triisopropyl-[1,r-biphenyl]-2-yl)phosphine, and 10.64 g (32.6 mmol) cesium carbonate were added to this solution and the resulting mixture stirred at 115°C for 15 min. Then, 3-((tert-butoxycarbonyl)amino)azetidin-l-ium chloride was added and the reaction mixture stirred for 1.5 h at 115 °C. The mixture was cooled to room temperature, the solvent was evaporated, and the residue extracted between water and ethyl acetate. The organic phase was washed with water and brine, dried over MgSO$_4$, filtered, and evaporated. The crude material was purified by flash chromatography to yield 7.8 g (12.15 mmol, 93%) of the desired product.

ESI-MS [M+H$^+$] = 482  Calculated for C$_{27}$H$_{35}$N$_3$O$_5$ = 481.11

11.3 Cis-ethyl (6-(3-aminoazetidin-l -yl)-4-benzylchroman-3-yl)carbamate

![Chemical structure](image)

7.8 g (12.15 mmol) of cis-tert-butyl (1-(3-(azetidin-1-yl)-4-benzyl-3-((ethoxycarbonyl)amino)chroman-6-yl carbamate were dissolved in methylene chloride, 9.0 mL (117 mmol) trifluoroacetic acid were added, and the reaction mixture stirred at room temperature over night. The solvent was evaporated, the residue dissolved in water and washed with methyl tert-butylether. The organic layer was washed with water additional 3x. To the combined water layers aqueous sodium bicarbonate solution was added until pH 8 was reached and extracted with methylene chloride (3x). The combined methylene dichloride extracts were dried over MgSO$_4$ and concentrated to yield 4.33 g (11.35 mmol, 93%).
11.4 Cis-ethyl (-4-benzyl-6-(3-(propylsulfonamido)azetidin-1-yl)chroman-3-yl)carbamate

![Chemical structure of cis-ethyl (-4-benzyl-6-(3-(propylsulfonamido)azetidin-1-yl)chroman-3-yl)carbamate]

1.5 g (3.93 mmol) of cis-ethyl (-6-(3-aminoazetidin-1-yl)-4-benzylchroman-3-yl)carbamate were dissolved in methylene dichloride, 1.2 g (9.83 mmol) N,N-dimethylpyridin-4-amine, and 0.60 mL (5.39 mmol) propane-1-sulfonyl chloride were added. The reaction mixture was stirred for 1 h at room temperature. The solvent was evaporated and the residue partitioned between ethyl acetate and water. The organic layer was washed twice with water and once with brine, dried over MgSO₄, filtrated, and concentrated. The crude material was purified by flash chromatography to yield 1.74 g (3.57 mmol, 91%) of the desired product.

ESI-MS [M+H⁺] = 382 Calculated for C₂₂H₂₇N₃O₅S = 381.

11.5 Cis-ethyl (-4-benzyl-6-(3-(propylsulfonamido)azetidin-1-yl)chroman-3-yl)carbamate

![Chemical structure of cis-ethyl (-4-benzyl-6-(3-(propylsulfonamido)azetidin-1-yl)chroman-3-yl)carbamate]

1.74 g (3.57 mmol) of cis-ethyl (-4-benzyl-6-(3-(propylsulfonamido)azetidin-1-yl)chroman-3-yl)carbamate were dissolved in tetrahydrofuran under nitrogen atmosphere, 18 mL (18 mmol) lithium aluminium hydride solution (1 M in tetrahydrofuran) were added, and the reaction mixture stirred at reflux for 1 h. The reaction mixture was cooled to room temperature, the excess of lithium aluminium hydride quenched with methanol, and the solvent was evaporated. The residue was partitioned between ethyl acetate and water. The resulting mixture was filtered through celite. Filtrate: aqueous layer was separated and extracted with ethyl acetate. The combined organic layers were dried over MgSO₄, filtered, and concentrated. The crude material was purified by flash chromatography to yield 1.42 g (3.32 mmol, 93%) of the desired product.

ESI-MS [M+H⁺] = 430 Calculated for C₂₃H₃₁N₃O₃S = 429.

Example 12: Cis-N-(1-(-4-benzyl-3-(methylamino)chroman-6-yl)azetidin-3-yl)ethanesulfonamide
Cis-N-(1-(-4-benzyl-3-(methylamino)chroman-6-yl)azetidin-3-yl)ethanesulfonamide was prepared in analogy to example 11.

ESI-MS [M+H+] = 416 Calculated for C22H29N3O3S = 415.

Example 13: Cis-N-(1 -(-4-benzyl-3-(methylamino)chroman-6-yl)azetidin-3-yl)-l-cyclopropylmethanesulfonamide

Cis-N-(1 -(-4-benzyl-3-(methylamino)chroman-6-yl)azetidin-3-yl)-l-cyclopropylmethanesulfonamide was prepared in analogy to example 11.

ESI-MS [M+H+] = 442 Calculated for C24H31N3O3S = 441.

Example 14: Cis-N-(1 -(-4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)ethanesulfonamide and trans-N-(1 -(-4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)ethanesulfonamide

Cis-N-(1 -(-4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)ethanesulfonamide and trans-N-(1 -(-4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)ethanesulfonamide were prepared in analogy to example 11.

Example 15: Cis-N-(l-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)-l-methyl-lH-imidazole-4-sulfonamide and trans-N-(l-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)- l-methyl- lH-imidazole-4-sulfonamide

Cis-N-(l-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)-l-methyl-lH-imidazole-4-sulfonamide and trans-N-(l-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)- l-methyl- lH-imidazole-4-sulfonamide were prepared in analogy to example 11.


Example 16: Cis-N-(l-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)propane-1-sulfonamide and trans-N-(l-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)propane-1-sulfonamide

Cis-N-(l-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)propane-1-sulfonamide and trans-N-(l-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)propane-1-sulfonamide were prepared in analogy to example 11.


Example 17: Cis-N-(l-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)-l-methyl-lH-pyrazole-4-sulfonamide and trans-N-(l-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)- l-methyl- lH-pyrazole-4-sulfonamide
Cis-N-(1-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)-l-methyl-1H-pyrazole-4-sulfonamide and trans-N-(l-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)-l-methyl-1H-pyrazole-4-sulfonamide were prepared in analogy to example 11.

17a. Cis-isomer: ESI-MS [M+H+] = 486 Calculated for C_{24}H_{24}F_{5}N_{6}O_{3}S = 485.
17b. Trans-isomer: ESI-MS [M+H+] = 486 Calculated for C_{24}H_{24}F_{5}N_{6}O_{3}S = 485.

Example 18: Cis-N-(l-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)-l-methyl-1H-1,2,3-triazole-4-sulfonamide and trans-N-(l-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)-l-methyl-1H-1,2,3-triazole-4-sulfonamide

18a. Cis-isomer: ESI-MS [M+H+] = 487 Calculated for C_{23}H_{27}FN_{6}O_{3}S = 486.
18b. Trans-isomer: ESI-MS [M+H+] = 487 Calculated for C_{23}H_{27}FN_{6}O_{3}S = 486.

Example 19: Cis-N-(l-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)-l-cyclopropylmethanesulfonamide and trans-N-(l-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)-l-cyclopropylmethanesulfonamide
Cis-N-(1-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)-l-cyclopropylmethanesulfonamide and trans-N-(1-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)-l-cyclopropylmethanesulfonamide were prepared in analogy to example 11.

19a. Cis-isomer: ESI-MS [M+H+] = 460 Calculated for C_{24}H_{30}F_{N}O_{3}S = 459.
19b. Trans-isomer: ESI-MS [M+H+] = 460 Calculated for C_{24}H_{30}F_{N}O_{3}S = 459.

Example 20: Cis-N-(1-(3-amino-4-benzylchroman-6-yl)azetidin-3-yl)propane-1-sulfonamide

0.04 g (0.08 mmol) of cis-ethyl (4-benzyl-6-(3-(propylsulfonamido)azetidin-1-yl)chroman-3-yl)carbamate (Example 11, 11.4) were dissolved in ethanolic potassium hydroxide solution (20%) and stirred at 90°C in the microwave for 15 min. The solvent was evaporated and the residue partitioned between ethyl acetate and water. The organic layer was washed twice with water and the combined water layers were extracted another 2x with ethyl acetate. The combined ethyl acetate extracts were dried over MgSO₄, filtrated, and concentrated. The crude material was purified by flash chromatography to yield 0.03 g (0.06 mmol, 82%) of the desired product.

ESI-MS [M+H+] = 416 Calculated for C_{22}H_{29}N_{3}O_{3}S = 415.

Example 21: Cis-N-(1-(3-amino-4-benzylchroman-6-yl)azetidin-3-yl)-l-cyclopropylmethanesulfonamide

Cis-N-(l-(3-amino-4-benzylchroman-6-yl)azetidin-3-yl)-l-cyclopropylmethanesulfonamide was prepared in analogy to example 20.

ESI-MS [M+H+] = 428 Calculated for C_{23}H_{29}N_{3}O_{3}S = 427.

Example 22: Cis-N-(l-(4-benzyl-3-(methylamino)chroman-6-yl)azetidin-3-yl)propane-1-sulfonamide - Isomer 1
Cis-N-(l-(4-benzyl-3-(methylamino)chroman-6-yl)azetidin-3-yl)propane-1-sulfonamide was prepared by separation of the racemic mixture obtained in example 11 through chiral chromatography on Daicel Chiralpak (n-heptane ethanol 65:35 + 0.1% triethylamine) and isolation of the isomer as the first eluting peak.

ESI-MS [M+H+] = 430  Calculated for C_{23}H_{31}N_{3}O_{3}S = 429.

Example 23: Cis-N-(l-(4-benzyl-3-(methylamino)chroman-6-yl)azetidin-3-yl)propane-1-sulfonamide - Isomer 2

Cis-N-(l-(4-benzyl-3-(methylamino)chroman-6-yl)azetidin-3-yl)propane-1-sulfonamide was prepared by separation of the racemic mixture obtained in example 11 through chiral chromatography on Daicel Chiralpak (n-heptane ethanol 65:35 + 0.1%, triethylamine) and isolation of the isomer as the second eluting peak.

ESI-MS [M+H+] = 430  Calculated for C_{23}H_{31}N_{3}O_{3}S = 429.

Example 24: Cis-N-(l-(4-benzyl-3-(methylamino)chroman-6-yl)azetidin-3-yl)-l-cyclopropylmethanesulfonamide - Isomer 1

Cis-N-(1-(4-benzyl-3-(methylamino)chroman-6-yl)azetidin-3-y)-l-cyclopropylmethanesulfonamide was prepared by separation of the racemic mixture obtained in example 13 through chiral chromatography on Daicel Chiralpak (n-heptane ethanol 65:35 + 0.1% triethylamine) and isolation of the isomer as the first eluting peak.
ESI-MS [M+H+] = 442 Calculated for C_{24}H_{31}N_{3}O_{3}S = 441.

Example 25: Cis-N-(l-(4-benzyl-3-(methylamino)chroman-6-yl)azetidin-3-yl)-l-cyclopropylmethanesulfonamide – Isomer 2

Cis-N-(1-(4-benzyl-3-(methylamino)chroman-6-yl)azetidin-3-yl)-l-cyclopropylmethanesulfonamide was prepared by separation of the racemic mixture obtained in example 13 through chiral chromatography on Daicel Chiralpak (n-heptane ethanol 65:35 + 0.1% triethylamine) and isolation of the isomer as the second eluting peak.

ESI-MS [M+H+] = 442 Calculated for C_{24}H_{31}N_{3}O_{3}S = 441.

Example 26: Cis-l-(4-benzyl-7-fluoro-6-(3-(5-fluoropyridine-3-sulfonamido)azetidin-1-yl)chroman-3-yl)azetidin-l-ium (E)-3-carboxyacrylate

Cis-l-(4-benzyl-7-fluoro-6-(3-(5-fluoropyridine-3-sulfonamido)azetidin-1-yl)chroman-3-yl)azetidin-l-ium (E)-3-carboxyacrylate was prepared in analogy to example 1.

ESI-MS [M+H+] = 527 Calculated for C_{27}H_{28}F_{2}N_{4}O_{3}S = 526.

Example 27: Cis-N-(l-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)propane-l-sulfonamide - Isomer 1
Cis-N-(1-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)propane-1-sulfonamide was prepared by separation of the racemic mixture obtained in example 16 through chiral chromatography on Daicel Chiralpak (n-heptane ethanol 70:30 + 0.1% triethylamine) and isolation of the isomer as the first eluting peak.

ESI-MS [M+H]+ = 448 Calculated for C_{23}H_{30}FN_{3}O_{3}S = 429.

Example 28: Cis-N-(1-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)propane-1-sulfonamide - Isomer 2

Cis-N-(1-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)propane-1-sulfonamide was prepared by separation of the racemic mixture obtained in example 11 through chiral chromatography on Daicel Chiralpak (n-heptane ethanol 65:35 + 0.1% triethylamine) and isolation of the isomer as the second eluting peak.

ESI-MS [M+H]+ = 448 Calculated for C_{23}H_{30}FN_{3}O_{3}S = 429.

Example 29: Cis-N-(1-(4-benzyl-3-(propylamino)chroman-6-yl)azetidin-3-yl)propane-1-sulfonamide

0.17 g (0.41 mmol) of cis-N-(1-(3-amino-4-benzylchroman-6-yl)azetidin-3-yl)propane-1-sulfonamide was reacted with 0.03 mL (0.41 mmol) propionaldehyde in the presence of 0.02 mL (0.41 mol) glacial acetic acid in 20 mL dichloro ethylene. 0.03 g (0.51 mmol) sodiumcyanoborohydride were dissolved in 5 mL methanol, added, and the mixture was stirred at room temperature for 30 min. The reaction mixture was added to aqueous sodium bicarbonate solution and stirred for 15 min., then it was extracted three times with dichloro methane. The combined organic phases were dried with MgSO_4 and evaporated to dryness. The residue was purified by flash chromatography to yield 0.09 g (0.19 mmol, 47 %) of the desired product.

ESI-MS [M+H]+ = 458 Calculated for C_{25}H_{35}N_{3}O_{3}S = 457.

Example 30: Cis-N-(1-(4-benzyl-3-(diethylamino)chroman-6-yl)azetidin-3-yl)propane-1-sulfonamide
Cis-N-(l-(4-benzyl-3-(diethylamino)chroman-6-yl)azetidin-3-yl)propane-1-sulfonamide was prepared in analogy to example 29.

ESI-MS [M+H+] = 472  Calculated for C\textsubscript{26}H\textsubscript{37}N\textsubscript{3}O\textsubscript{3}S = 471.

Example 31: Cis-N-(l-(4-benzyl-3-((cyclopropylmethyl)amino)chroman-6-yl)azetidin-3-yl)propane-1-sulfonamide

Cis-N-(l-(4-benzyl-3-((cyclopropylmethyl)amino)chroman-6-yl)azetidin-3-yl)propane-1-sulfonamide was prepared in analogy to example 29.

ESI-MS [M+H+] = 470  Calculated for C\textsubscript{26}H\textsubscript{35}N\textsubscript{3}O\textsubscript{3}S = 469.

Example 32: Cis-N-(l-(4-benzyl-3-(cyclobutylamino)chroman-6-yl)azetidin-3-yl)propane-1-sulfonamide

Cis-N-(l-(4-benzyl-3-(cyclobutylamino)chroman-6-yl)azetidin-3-yl)propane-1-sulfonamide was prepared in analogy to example 29.

ESI-MS [M+H+] = 470  Calculated for C\textsubscript{26}H\textsubscript{35}N\textsubscript{3}O\textsubscript{3}S = 469.

Biological testing

1. [\textsuperscript{3}H]-Glycine uptake into recombinant CHO cells expressing human GlyT\textsubscript{1}:
Human GlyTlc expressing recombinant hGlyTlc_5_CHO cells were plated at 20,000 cells per well in 96 well Cytostar-T scintillation microplates (Amersham Biosciences) and cultured to sub-confluency for 24 h. For glycine uptake assays the culture medium was aspirated and the cells were washed once with 100 µl HBSS (Gibco BRL, #14025-050) with 5 mM L-Alanine (Merck #1007). 80 µl HBSS buffer were added, followed by 10 µl inhibitor or vehicle (10% DMSO) and 10 µl [H]-glycine (TRK71, Amersham Biosciences) to a final concentration of 200 nM for initiation of glycine uptake. The plates were placed in a Wallac Microbeta (PerkinElmer) and continuously counted by solid phase scintillation spectrometry during up to 3 hours. Nonspecific uptake was determined in the presence of 10 µM Org24598. IC₅₀ calculations were made by four-parametric logistic nonlinear regression analysis (GraphPad Prism) using determinations within the range of linear increase of [H]-glycine incorporation between 60 and 120 min.

2. Radioligand binding assays using recombinant CHO cell membranes expressing human GlyT1:

Radioligand binding to human GlyTlc transporter-expressing membranes was determined as described in Mezler et al., Molecular Pharmacology 74:1705-1715, 2008.

The following results were obtained with the compounds disclosed in the examples:

<table>
<thead>
<tr>
<th>Example</th>
<th>radioligand binding (Kₛₛₛ [µM])</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>2 *</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>3</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>4</td>
<td>&lt;0.1</td>
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<td>5</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>7 *</td>
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</tr>
<tr>
<td>8 *</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>9</td>
<td>&lt;1.0</td>
</tr>
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<td>11</td>
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</tr>
<tr>
<td>12</td>
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<tr>
<td>13</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>14a</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>14b</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>15a</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>15b</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>16a</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
16b <0.01
17a <0.01
17b <0.01
18a <0.01
18b <0.01
19a <0.01
19b <0.01
20* <0.1
21* <0.01
22* <0.01
23* <1.0
24 <0.01
25* <1.0
26* <0.1
27 <0.01
28 <0.1
29 <0.1
30 <0.1
31 <1.0
32 <1.0

* these compounds were tested in the form of the corresponding fumarate salts

3. Metabolic stability

Metabolic stability was determined as follows:

0.5 µM test substance was preincubated together with human liver microsomes (0.25 mg of microsomal protein/ml) in 0.05 M potassium phosphate buffer of pH 7.4 in microtiter plates at 37°C for 5 min. The reaction was started by adding NADPH (1.0 mM). After 0, 5, 10, 15, 20 and 30 min the reaction was stopped and cooled with twice the amount of quench solution consisting of acetonitrile/methanol 1:1, and containing 0.2 µM carbutamide. The samples were frozen until analyzed. The remaining concentration of undegraded test substance was determined by LC MSMS. The half-life (T1/2) was determined from the gradient of the signal of test substance/unit time plot, allowing to calculate the half-life of the test substance, assuming first order kinetics, from the decrease in the concentration of the compound with time. The microsomal clearance (mClint) was calculated as follows: 

\[ m\text{Clint} = \frac{(\ln(2)/t_{1/2})}{\text{Microsomal Protein Concentration (mg/ml))} \times 1000 \] 

leading to the unit of uL/min/mg. The scaled clearance (mClint_scaled) was calculated as

\[ m\text{Clint}_{\text{scaled}} = m\text{Clint} \times (\text{Microsomal Yield (mg/kg BW)})/1000000 \times 60, \] 

leading to the units L/hr/kg. The Microsomal Yield is defined by the specifics of the used microsomes. Calculations
The following results were obtained with the compounds disclosed in the examples:

<table>
<thead>
<tr>
<th>Example</th>
<th>human mCl [L/h/Kg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;5</td>
</tr>
<tr>
<td>2*</td>
<td>&lt;5</td>
</tr>
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<td>3</td>
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<td>8*</td>
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<tr>
<td>9</td>
<td>&lt;50</td>
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<td>14b</td>
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<td>16b</td>
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<td>17a</td>
<td>&lt;5</td>
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<td>17b</td>
<td>&lt;5</td>
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<tr>
<td>18a</td>
<td>&lt;50</td>
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<tr>
<td>18b</td>
<td>&lt;5</td>
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<td>&lt;50</td>
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<tr>
<td>28</td>
<td>&lt;5</td>
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<tr>
<td>29</td>
<td>&lt;5</td>
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<tr>
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<td>&lt;50</td>
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<tr>
<td>31</td>
<td>&lt;5</td>
</tr>
<tr>
<td>32</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

*These compounds were tested in the form of the corresponding fumarate salts.

4. Determination of efflux ratio using Madin-Darby Canine Kidney Type II cells

5. Bidirectional transport experiments were performed on Madin-Darby Canine Kidney Type II cells over-expressing multidrug resistance protein 1 (MDR1-MDCK) to evaluate the compounds as potential P-gp substrates.

Compounds were added at 1 μM in HBSS-pH 7.4 (hanks balanced salt solution) to either the apical or basolateral side of MDR1-MDCK cell monolayers grown on Millicell 96-Cell polycarbonate filters. Samples were collected from both apical and basolateral sides at time 0 and after 1h incubation at 37C, compounds concentrations were measured by HPLC/MS/MS and permeability coefficients were then determined in both transport directions. The efflux ratio was subsequently calculated from the permeability coefficient.
We claim:

1. Compounds of the formula (I)

\[
\text{A} \quad \text{is a 5- or 6-membered ring;}
\]

\[
R^1 \quad \text{is hydrogen, } \text{C}_6^6\text{-alkyl, } \text{C}_3\text{-C}_2\text{-cycloalkyl-Ci-C}_6^6\text{-alkyl, halogenated } \text{C}_6^6\text{-alkyl, tri-(Ci-C}_4^4\text{-alkyl)-silyl-Ci-C}_4^4\text{-alkyl, hydroxy-Ci-C}_4^4\text{-alkyl, Ci-C}_6^6\text{-alkoxy-Ci-C}_4^4\text{-alkyl, amino-Ci-C}_4^4\text{-alkyl, Ci-C}_6^6\text{-alkylamino-Ci-C}_4^4\text{-alkyl, di-Ci-C}_6^6\text{-alkylamino-Ci-C}_4^4\text{-alkyl, Ci-C}_6^6\text{-alkylcarbonylamino-Ci-C}_4^4\text{-alkyl, Ci-C}_6^6\text{-alkylaminocarboxylamino-Ci-C}_4^4\text{-alkyl, Ci-C}_6^6\text{-alkylsulfonylamino-Ci-C}_4^4\text{-alkyl, (optionally substituted C}_6^6\text{-C}_1^2\text{-aryl-Ci-C}_6^6\text{-alkyl)amino-Ci-C}_4^4\text{-alkyl, optionally substituted C}_6^6\text{-C}_1^2\text{-aryl-Ci-C}_4^4\text{-alkyl, optionally substituted } \text{M}_3^3\text{-M}_2^2\text{-heterocyclyl-Ci-C}_4^4\text{-alkyl, C}_3^3\text{-C}_2^2\text{-cycloalkyl, Ci-C}_6^6\text{-alkylcarbonyl, d-C}_6^6\text{-alkoxycarbonyl, halogenated Ci-C}_6^6\text{-alkoxycarbonyl, C}_6^6\text{-C}_1^2\text{-arylaminocarbonyl, Ci-C}_6^6\text{-alkylaminocarbonyl, (halogenated Ci-C}_4^4\text{-alkyl)aminocarbonyl, Ci-C}_2^2\text{-arylaminocarbonyl, C}_2^2\text{-C}_6^6\text{-alkenyl, C}_2^2\text{-C}_6^6\text{-alkynyl, optionally substituted C}_6^6\text{-C}_1^2^2\text{-aryl, hydroxy, Ci-C}_6^6\text{-alkoxy, halogenated Ci-C}_6^6\text{-alkoxy, Ci-C}_6^6\text{-hydroxyalkoxy, Ci-C}_6^6\text{-alkoxy-Ci-C}_4^4\text{-alkoxy, amino-Ci-C}_4^4\text{-alkoxy, Ci-C}_6^6\text{-alkylamino-Ci-C}_4^4\text{-alkoxy, di-Ci-C}_6^6\text{-alkylamino-Ci-C}_4^4\text{-alkoxy, Ci-C}_6^6\text{-alkylcarbonylamino-Ci-C}_4^4\text{-alkoxy, C}_6^6\text{-C}_1^2^2\text{-arylcarbonylamino-Ci-C}_4^4\text{-alkoxy, Ci-C}_6^6\text{-alkoxycarbonylamino-Ci-C}_4^4\text{-alkoxy, (halogenated Ci-C}_4^4\text{-alkyl)sulfonylamino-Ci-C}_4^4\text{-alkoxy, C}_6^6\text{-C}_1^2\text{-aryl-Ci-C}_6^6\text{-alkylsulfonylamino-Ci-C}_4^4\text{-alkoxy, (Ce-C}_4^4^\text{-aryl-Ci-C}_6^6\text{-alkyl)sulfonylamino-Ci-C}_4^4\text{-alkoxy, M}_3^3\text{-M}_2^2\text{-heterocyclsulfonylamino-Ci-C}_4^4\text{-alkoxy, M}_3^3\text{-M}_2^2\text{-heterocyclsulfonylamino-Ci-C}_4^4\text{-alkoxy, C}_6^6\text{-C}_1^2^2\text{-aryloxy, M}_3^3\text{-M}_2^2\text{-aryloxy, M}_3^3\text{-M}_2^2\text{-aryloxy, C}_6^6\text{-C}_1^2^2\text{-aryloxy, halogenated Ci-C}_6^6\text{-alkylthio, halogenated Ci-C}_6^6\text{-alkylthio, Ci-C}_6^6\text{-alkylamino, (halogenated Ci-C}_6^6\text{-alkyl)amino, di-Ci-C}_6^6\text{-alkylamino, di-(halogenated Ci-C}_6^6\text{-alkyl)amino, Ci-C}_6^6\text{-alkylcarbonylamino, (halogenated Ci-C}_6^6\text{-alkyl)carbonylamino, Ce-C}_4^4^-}
\]
arylcarbonylamino, Ci-C6-alkylsulfonylamino, (halogenated Ci-C6-alkyl)sulfonylamino, C6-C2-arylsulfonylamino or optionally substituted M3-M12-heterocycl;

W is -NR 7- or a bond;

5

A1 is optionally substituted Ci-C4-alkylene or a bond;

Q is -S(0) 2- or -C(O)-;

10

Y is -NR 8- or a bond;

n1 is 0, 1, 2, or 3;

n2 is 0, 1, 2, or 3;

15

X1 is >N- or >CH-;

R6 is hydrogen, halogen, Ci-C4-alkyl, halogenated Ci-C4-alkyl, -CN, OH Ci-C6-alkoxy or halogenated Ci-C6-alkoxy, or two radicals R6 together with the carbon atom to which they are attached form a carbonyl group;

20

R2 is hydrogen, halogen, Ci-C6-alkyl, halogenated Ci-C4-alkyl, -CN, C2-C6-alkenyl, C2-C6-alkynyl, optionally substituted C6-C2-aryl, hydroxy, Ci-C6-alkoxy, halogenated C1-C6-alkoxy, Ci-C6-alkoxycarbonyl, C2-C6-alkenylxy, C6-C2aryl-Ci-C4-alkoxy, C1-C6-alkylcarbonyloxy, Ci-C6-alkylthio, Ci-C6-alkylsulfynil, Ci-C6-alkylsulfonil, aminosulfonyl, amino, Ci-C6-alkylamino, C2-C6-alkenylamino, nitro or optionally substituted M1-M12-heterocycl, or two radicals R2 together with the ring atoms of A to which they are bound form a 5- or 6 membered ring;

25

A2 is -O-, -S- or -NR 9-;

30

R3 is hydrogen, halogen, Ci-C6-alkyl or Ci-C6-alkoxy, or two radicals R3 together with the carbon atom to which they are attached form a carbonyl group;

35

Y1 is a bond or optionally substituted Ci-C4-alkylene;

40

R2a is hydrogen, Ci-C6-alkyl, C3-C2-cycloalkyl-Ci-C4-alkyl, halogenated Ci-C4-alkyl, hydroxy-C4-alkyl, Ci-C6alkoxy-Ci-C4-alkyl, amino-Ci-C4-alkyl, -CH2CN, C6-C2aryl-Ci-C4-alkyl, optionally substituted C3-C2-cycloalkyl, -CHO, Ci-C4-alkylecarbonyl, (halogenated Ci-C4-alkyl)carbonyl, C6-C2arylcarbonyl, Ci-C4-alkoxycarbonyl, C6-C12-
aryloxycarbonyl, Ci-C₆-alkylaminocarbonyl, C₂-C₆-alkenyl, -C(=NH)NH₂, -C(=NH)NHCN, Ci-C₆-alkylsulfonyl, C₆-C₁₂-arylsulfonyl, amino, -NO or optionally substituted M₃-M₁₂-heterocyclyl; or

R⁴ is optionally substituted Ci-C₄-alkylene that is bound to a carbon atom in Y¹;

R⁴ is hydrogen, Ci-C₆-alkyl, halogenated Ci-C₄-alkyl, hydroxy-Ci-C₄-alkyl, Ci-C₆-alkoxy-Ci-C₄-alkyl, amino-Ci-C₄-alkyl, -CH₂CN, -CHO, Ci-C₄-alkylcarbonyl, (halogenated Ci-C₄-alkyl)carbonyl, C₆-C₁₂-arylcarbonyl, Ci-C₄-alkoxycarbonyl, (halogenated Ci-C₄-alkyl)carbonyl, C₆-C₁₂-aryloxycarbonyl, Ci-C₆-alkylaminocarbonyl, C₂-C₆-alkenyl, -C(=NH)NH₂, -C(=NH)NHCN, Ci-C₆-alkylsulfonyl, C₆-C₁₂-arylsulfonyl, amino, -NO or M₃-M₁₂-heterocyclyl; or

R⁴, R⁴b together are optionally substituted C₂-C₆-alkylene, wherein one -CH₂⁻ of C₂-C₆-alkylene may be replaced by an oxygen atom or -NR⁰⁻;

X² is -O-, -NR¹⁻, -S-, >CR²⁻R²b or a bond;

X³ is -O-, -NR²⁻, -S-, >CR³⁻R³b or a bond;

R⁵ is optionally substituted C₆-C₁₂-aryl, optionally substituted C₃-C₁₂-cycloalkyl or optionally substituted M₃-M₁₂-heterocyclyl;

R⁷ is hydrogen or Ci-C₆-alkyl;

R⁸ is hydrogen, Ci-C₆-alkyl, C₃-C₁₂-cycloalkyl, amino-Ci-C₆-alkyl, optionally substituted C₆-C₁₂-aryl-Ci-C₄-alkyl or M₃-M₁₂-heterocyclyl; or

R⁹ is hydrogen, Ci-C₆-alkyl, C₃-C₁₂-cycloalkyl-Ci-C₄-alkyl, halogenated Ci-C₄-alkyl, hydroxy-Ci-C₄-alkyl, Ci-C₆-alkoxy-Ci-C₄-alkyl, amino-Ci-C₄-alkyl, CH₂CN, C₆-C₁₂-aryl-Ci-C₄-alkyl, C₃-C₁₂-cycloalkyl, -CHO, Ci-C₄-alkylcarbonyl, (halogenated C₆-C₄-alkyl)carbonyl, C₆-C₁₂-arylcarbonyl, Ci-C₆-alkylaminocarbonyl, C₂-C₆-alkenyl, -C(=NH)NH₂, -C(=NH)NHCN, C₁-C₆-alkylsulfonyl, C₆-C₁₂-arylsulfonyl, amino, -NO or M₃-M₁₂-heterocyclyl;

R¹⁰ is hydrogen or C₁-C₆-alkyl;
\[ R^{1a} \text{ is hydrogen or } \text{Ci-C6-alkyl}; \]
\[ R^{1b} \text{ is hydrogen or } \text{Ci-C6-alkyl}; \]
\[ R^{12a} \text{ is hydrogen, optionally substituted } \text{Ci-C6-alkyl, Ci-C6-alkylamino-Ci-C4-alkyl, di-Cp C}_6\text{-alkylamino-Ci-C4-alkyl, M}_3\text{-M}_2\text{-heterocyclyl-Ci-C6-alkyl, optionally substituted } C_6\text{-Ci2-aryl or hydroxy; } \]
\[ R^{12b} \text{ is hydrogen or } \text{Ci-C6-alkyl, or } \]
\[ R^{12a}, R^{12b} \text{ together with the carbon atom to which they are attached form a carbonyl or are optionally substituted } C_2\text{-C4-alkylene, wherein one } -\text{CH}_2- \text{ of } C_2\text{-C4-alkylene may be replaced by an oxygen atom or } -\text{NR}^{14}-; \]
\[ R^{13a} \text{ is hydrogen, optionally substituted } \text{Ci-C6-alkyl, Ci-C6-alkylamino-Ci-C4-alkyl, di-Cp C}_6\text{-alkylamino-Ci-C4-alkyl, M}_3\text{-M}_2\text{-heterocyclyl-Ci-C6-alkyl, optionally substituted } C_6\text{-Ci2-aryl or hydroxy; } \]
\[ R^{13b} \text{ is hydrogen or } \text{Ci-C6-alkyl, or } \]
\[ R^{13a}, R^{13b} \text{ together with the carbon atom to which they are attached form a carbonyl or are optionally substituted } C_2\text{-C4-alkylene, wherein one } -\text{CH}_2- \text{ of } C_2\text{-C4-alkylene may be replaced by an oxygen atom or } -\text{NR}^{15}-; \]
\[ R^{14} \text{ is hydrogen or } \text{Ci-C6-alkyl; and } \]
\[ R^{15} \text{ is hydrogen or } \text{Ci-C6-alkyl, } \]
\[ \text{or a physiologically tolerated salt thereof. } \]

2. Compound as claimed in claim 1, wherein A is a benzene ring or a ring selected from the group consisting of the following 5- or 6-membered heterocyclic rings:
3. Compound as claimed in claim 1 or 2, wherein $R^1$ is C1-C6-alkyl, C3-C12-cycloalkyl-C1-C4-alkyl, or C3-C12-cycloalkyl.

4. Compound as claimed in any one of claims 1 to 3, wherein $W$ is a bond and $A^1$ is a bond.

5. Compound as claimed in any one of claims 1 to 4, wherein $Q$ is -S(0)2-.

6. Compound as claimed in any one of claims 1 to 5, wherein $Y$ is -NR8-.

7. Compound as claimed in any one of claims 1 to 6, wherein at least one of $n1$ and $n2$ is 1, 2, or 3.

8. Compound as claimed in any one of claims 1 to 7, wherein the sum of $n1+n2$ is 2, 3, or 4.

9. Compound as claimed in any one of claims 1 to 6, wherein $X^1$ is >N-, $n1$ is 1, and $n2$ is 1; or $X^1$ is >CH-, $n1$ is 1, and $n2$ is 1.

10. Compound as claimed in any one of claims 1 to 9, wherein $R^6$ is hydrogen or C1-C4-alkyl, or two radicals $R^6$ together with the carbon atom to which they are attached form a carbonyl group.

11. Compound as claimed in any one of claims 1 to 10, having the formula
wherein $R_1$, $W$, $A_1$, $Q$, $Y$, $n_1$, $n_2$, $X_1$, $R_6$, $R_2$, $A_2$, $R_3$, $Y_1$, $R_4a$, $R_4b$, $X_2$, $X_3$, $R_5$ are as defined in any one of claims 1 to 10.

5 12. Compound as claimed in any one of claims 1 to 11, wherein $R_2$ is hydrogen or halogen.

13. Compound as claimed in claim 11 or 12, having one of the formulae
wherein $R_1$, $W$, $A_1$, $Q$, $Y$, $n_1$, $n_2$, $X_1$, $R_6$, $R_2$, $A_2$, $R_3$, $Y_1$, $R_4$, $R_4$, $X_2$, $X_3$, $R_5$ are as defined in any of claims 1 to 12.

14. Compound as claimed in any one of claims 1 to 13, wherein $A^2$ is $-O-$.  

15. Compound as claimed in any one of claims 1 to 14, wherein $R_3$ is hydrogen or $C_1$-$C_6$-alkyl.  

16. Compound as claimed in any one of claims 1 to 15, having the formula
wherein \( R^3_a, R^3_b, R^3_c, R^3_d \) independently have the meaning of \( R^3 \), and \( A, R^1, W, A^1, Q, Y, n_l, n_2, X^1, R^6, R^2, A^2, R^3, Y^1, R^{4a}, R^{4b}, X^2, X^3, R^5 \) are as defined in any one of claims 1 to 15.

17. Compound as claimed in claim 1 to 16, wherein \( Y^1 \) is a bond.

18. Compound as claimed in claim 1 to 17, wherein \( R^4_a \) is hydrogen, Ci-C6-alkyl, optionally substituted \( C_3-Ci_2 \)-cycloalkyl, \( C_3-Ci_2 \)-cycloalkyl-Ci-C4-alkyl, or \( M_3-M_{12} \)-heterocyclyl.

19. Compound as claimed in any one of claims 1 to 18, wherein \( R^4_b \) is hydrogen or Ci-C6-alkyl.

20. Compound as claimed in any one of claims 1 to 17, wherein \( R^4_a, R^4_b \) together are optionally substituted \( C_2-C_6 \) -alkylene, wherein one -CH\(_2\) of \( C_2-C_6 \) -alkylene may be replaced by an oxygen atom.

21. Compound as claimed in any one of claims 1 to 20, wherein \( X^2 \) is \( >CR^{12a}R^{12b} \).

22. Compound as claimed in any one of claims 1 to 21, wherein \( X^3 \) is a bond.

23. Compound as claimed in any one of claims 1 to 22, wherein \( R^{12a} \) is hydrogen or Ci-C6-alkyl and \( R^{12b} \) is hydrogen or Ci-C\(_6\)-alkyl.

24. Compound as claimed in any one of claims 1 to 23, wherein \( R^5 \) is optionally substituted aryl.

25. Compound as claimed in claim 24, having the formula
wherein \( A, R^1, W, A^1, Q, Y, n_1, n_2, X^1, R^6, R^2, R^3, A^2, Y^1, R^{4a}, R^{4b}, X^2, X^3 \) are as defined in any one of claims 1 to 23; and
\[ J, J^1, J^2, \ldots, J^{16} \]
are independently hydrogen, halogen, or halogenated C\textsubscript{i}-C\textsubscript{6}-alkyl.

26. Compound as claimed in any one of claims 1 to 25, wherein \( R^8 \) is hydrogen.

27. Compound as claimed in claim 1, wherein

\( A \) is a benzene ring;

\( R^1 \) is C\textsubscript{i}-C\textsubscript{6}-alkyl, C\textsubscript{3}-C\textsubscript{12}-cycloalkyl-Ci-C\textsubscript{4}-alkyl, or an optionally substituted M\textsubscript{3}-M\textsubscript{12}-heterocyclyl;

\( W \) is a bond;

\( A^1 \) is a bond;

\( Q \) is \(-S(0)_{2}-\);

\( Y \) is \(-NR^{8}_{-}\);

\( n_1 \) is 1;

\( n_2 \) is 1;
R^6 is hydrogen;

X^1 is ->N- or >CH-;

5 R^2 is hydrogen or halogen;

A^2 is -0-;

R^3 is hydrogen;

10 Y^1 is a bond;

R^{2a} is hydrogen, C1-C6-alkyl, C3-C12-cycloalkyl-C1-C4-alkyl, or C3-C12-cycloalkyl;

15 R^{2b} is hydrogen or C1-C6-alkyl; or

R^{2a}, R^{2b} together are C2-C6-alkylene;

20 X^2 is >CR^{12a}R^{12b};

X^3 is a bond;

R^5 is optionally substituted phenyl;

25 R^8 is hydrogen;

R^{12a} is hydrogen; and

30 R^{12b} is hydrogen.

28. The compound as claimed in claim 1 which is:

N-[1-[3-(azetidin-1-yl)-4-benzyl-chroman-6-yl]azetidin-3-yl]-1-methyl-imidazole-4-sulfonamide;

Cis-N-[1-(3-(azetidin-1-yl)-4-benzylchroman-6-yl)azetidin-3-yl]ethanesulfonamide;

Cis-N-[1-(3-(azetidin-1-yl)-4-benzylchroman-6-yl)azetidin-3-yl]propane-1-sulfonamide;

Cis-N-[1-(3-(azetidin-1-yl)-4-benzylchroman-6-yl)azetidin-3-yl]-1-cyclopropylmethanesulfonamide;

Cis-N-(1-(3-(azetidin-1-yl)-4-benzylchroman-6-yl)azetidin-3-yl)-1-methyl-1H-pyrazole-4-sulfonamide;
Cis-N-(1-(3-(azetidin-1-yl)-4-benzylchroman-6-yl)azetidin-3-yl)-1-methyl-1H-1,2,3-triazole-4-sulfonamide;
Cis-N-(1-(3-(azetidin-1-yl)-4-benzyl-7-fluorochroman-6-yl)azetidin-3-yl)-1-ethyl-1H-1,2,3-triazole-4-sulfonamide;
Cis-N-(1-(3-(azetidin-1-yl)-4-benzyl-7-fluorochroman-6-yl)azetidin-3-yl)-2-fluoropyridine-3-sulfonamide;
Cis-N-(1-(3-(azetidin-1-yl)-4-benzylchroman-6-yl)azetidin-3-yl)-2-fluoropyridine-3-sulfonamide;
Cis-N-(1-(4-benzyl-3-(methylamino)chroman-6-yl)azetidin-3-yl)propane-1-sulfonamide;
Cis-N-(1-(4-benzyl-3-(methylamino)chroman-6-yl)azetidin-3-yl)ethanesulfonamide;
Cis-N-(1-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)cyclopropylmethanesulfonamide;
Cis-N-(1-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)ethanesulfonamide;
Trans-N-(1-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)ethanesulfonamide;
Cis-N-(1-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)imidazole-4-sulfonamide;
Cis-N-(1-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)imidazole-4-sulfonamide;
Cis-N-(1-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)propane-1-sulfonamide;
Cis-N-(1-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)propane-1-sulfonamide;
Trans-N-(1-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)propane-1-sulfonamide;
Cis-N-(1-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)pyrazole-4-sulfonamide;
Trans-N-(1-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)pyrazole-4-sulfonamide;
Cis-N-(1-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)1H-1,2,3-triazole-4-sulfonamide;
Trans-N-(1-(4-benzyl-7-fluoro-3-(methylamino)chroman-6-yl)azetidin-3-yl)1H-1,2,3-triazole-4-sulfonamide;
Cis-N-(1-(3-amino-4-benzylchroman-6-yl)azetidin-3-yl)propane-1-sulfonamide;
Cis-N-(1-(3-amino-4-benzylchroman-6-yl)azetidin-3-yl)cyclopropylmethanesulfonamide;
Cis-1-(4-benzyl-7-fluoro-6-(3-(5-fluoropyridine-3-sulfonamido)azetidin-1-yl)chroman-3-yl)azetidin-1-ium (E)-3-carboxyacrylate;
Cis-N-(1-(4-benzyl-3-(propylamino)chroman-6-yl)azetidin-3-yl)propane-1-sulfonamide;
Cis-N-(1-(4-benzyl-3-(diethylamino)chroman-6-yl)azetidin-3-yl)propane-1-sulfonamide; and
Cis-N-(1-(4-benzyl-3-(cyclobutylamino)chroman-6-yl)azetidin-3-yl)sulfonamide, or a physiologically tolerated salt thereof.

29. The compound as claimed in any one of claims 1 to 28 for use in therapy.

30. Pharmaceutical composition which comprises a carrier and a compound of any one of claims 1 to 28.

31. A method for inhibiting the glycine transporter GlyT1 in a mammal in need thereof which comprises the administration of an effective amount of a compound of any one of claims 1 to 28.

32. The use of a compound of any one of claims 1 to 28 in the manufacture of a medicament for inhibiting the glycine transporter GlyT1.

33. A method for treating a neurologic or psychiatric disorder or pain in a mammalian patient in need thereof which comprises administering to the patient a therapeutically effective amount of a compound of any one of claims 1 to 28.

34. The use of a compound of any one of claims 1 to 28 in the manufacture of a medicament for treating a neurologic or psychiatric disorder or pain.

35. The compound of any one of claims 1 to 28 for use in a method of treating a neurologic or psychiatric disorder or pain.

36. The method, use or compound as claimed in any one of claims 30 to 35, wherein the disorder is associated with glycineric or glutamatergic neurotransmission dysfunction.

37. The method, use or compound as claimed in any one of claims 30 to 36, wherein the neurologic disorder is a cognitive disorder such as dementia, cognitive impairment, or attention deficit disorder.

38. The method, use or compound as claimed in claim 37, wherein the attention deficit disorder is an attention deficit disorder with hyperactivity.
39. The method, use or compound as claimed in any one of any one of claims 30 to 35, wherein the psychiatric disorder is an anxiety disorder, a mood disorder such as depression, a bipolar disorder, schizophrenia, or a psychotic disorder.
**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07D405/14 C07D311/58 C07D405/04 A61K31/352 A61P25/02

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols):

C07D A61K A61P

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

EPO-Internal, BIOSIS, CHEMABS Data, EMBASE, WPI Data, BEILSTEIN Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>WO 2013/020930 AI (ABBOTT GMBH &amp; CO KG [DE]; AMBERG WILHELM [DE]; LANGE UDO [DE]; POHLKI) 14 February 2013 (2013-02-14) cited in the application on claims 1,28,31; example 1; tables 1,2</td>
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Further documents are listed in the continuation of Box C.

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone.

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention.

"A" document member of the same patent family.

Date of the actual completion of the international search: 9 January 2015

Date of mailing of the international search report: 20/01/2015

Authorized officer: Hartinger, Stefan
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