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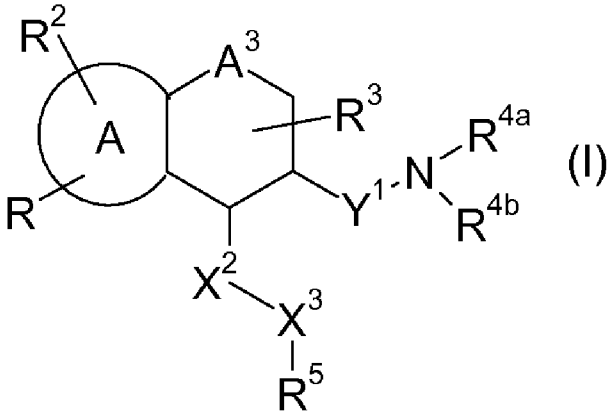
(54) **Title**: AMINOCHROMANE, AMINOTHIOCHROMANE AND AMINO-1,2,3,4-TETRAHYDROQUINOLINE DERIVATIVES, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM, AND THEIR USE IN THERAPY



(57) **Abstract**: The present invention relates to aminochromane, aminothiochromane and 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.

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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.

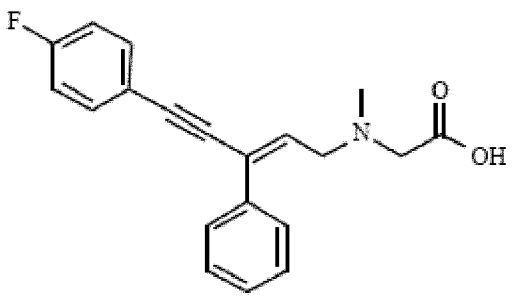
Two specific glycine transporters, GlyT1 and GlyT2 have been identified and shown to belong to the Na/Cl-dependent family of neurotransmitter transporters which includes taurine, gamma-aminobutyric acid (GABA), proline, monoamines and orphan transporters. GlyT1 and GlyT2 have been isolated from different 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 glycinergic 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 glycinergic 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 GlyT-1a, GlyT-1b and GlyT-1c, 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:



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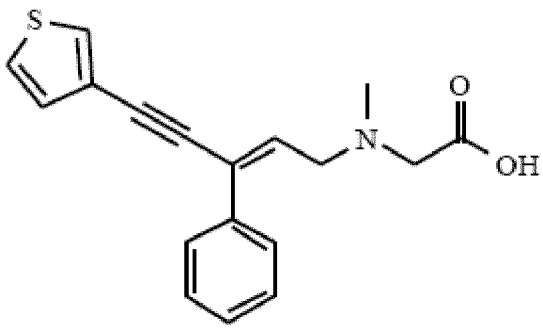

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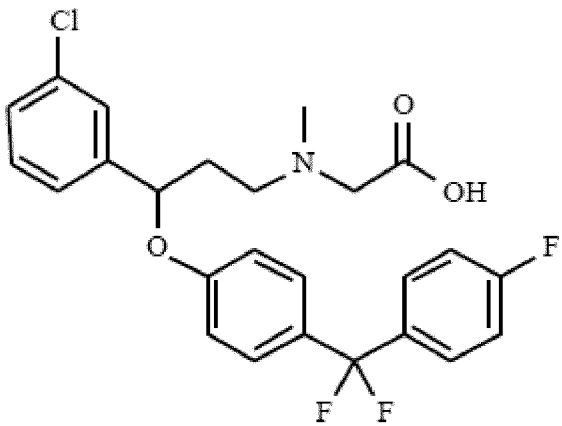

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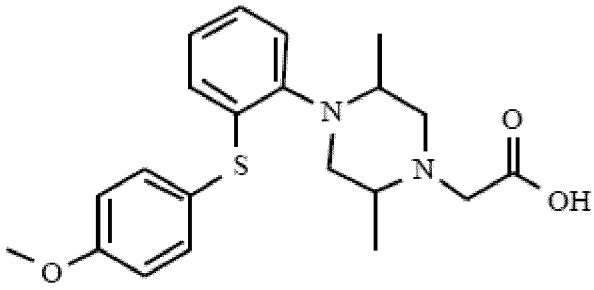

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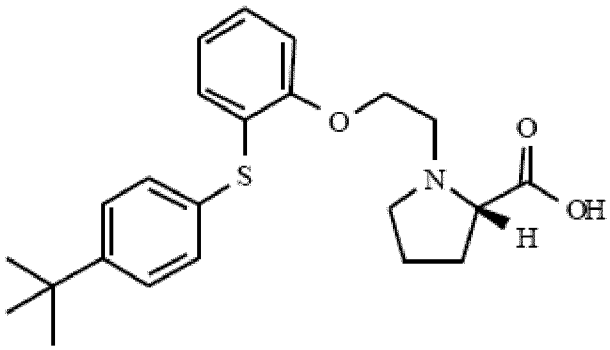

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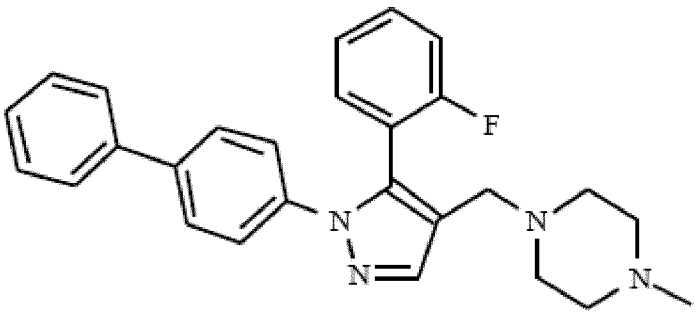

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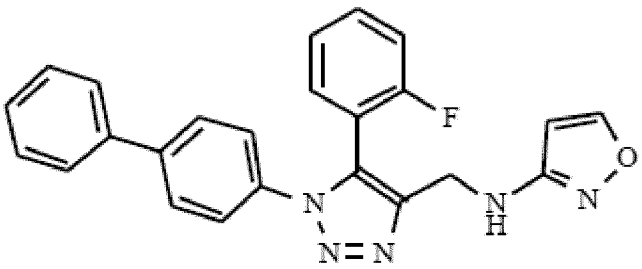

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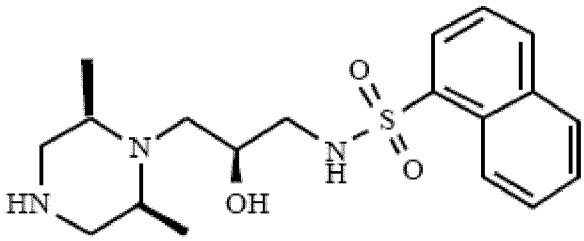

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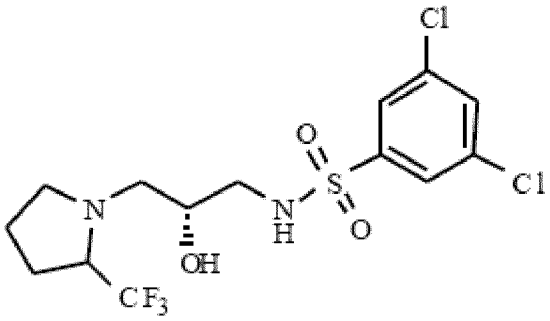

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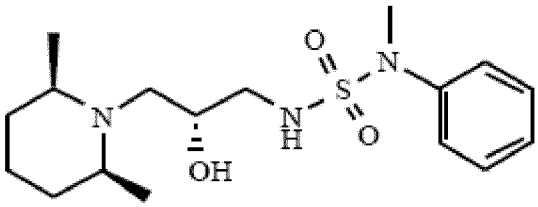

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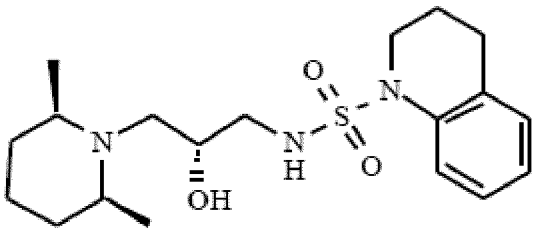

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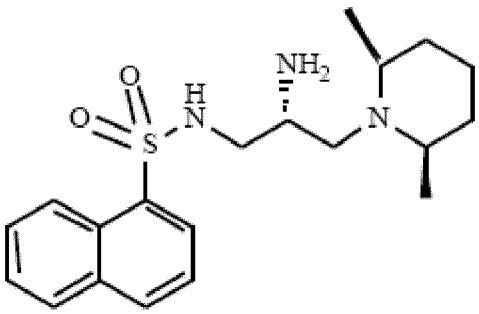

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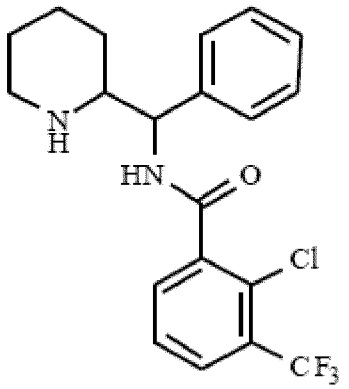

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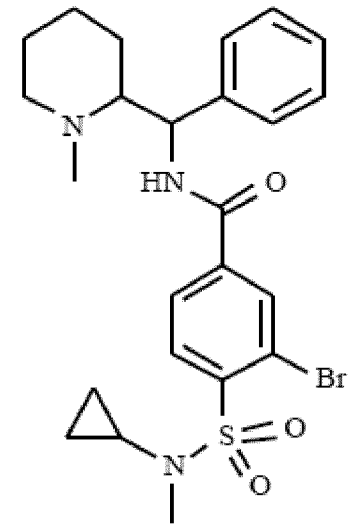

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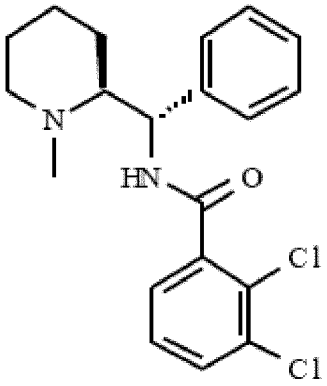

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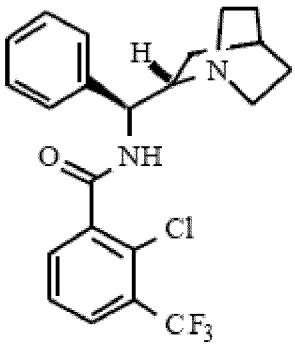

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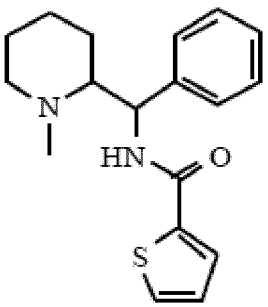

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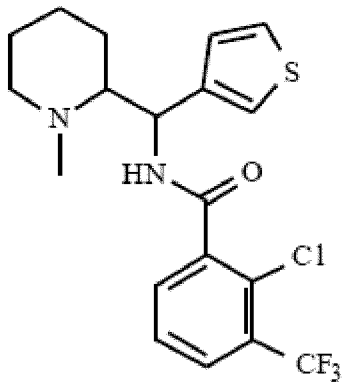

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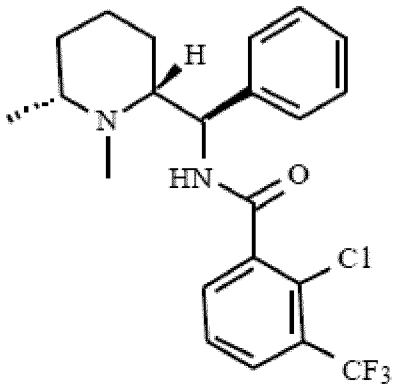

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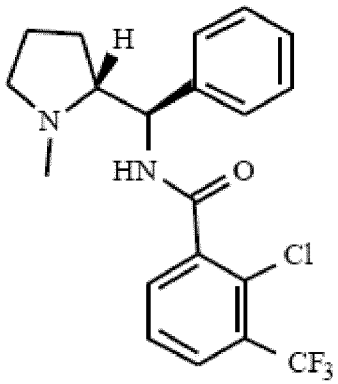

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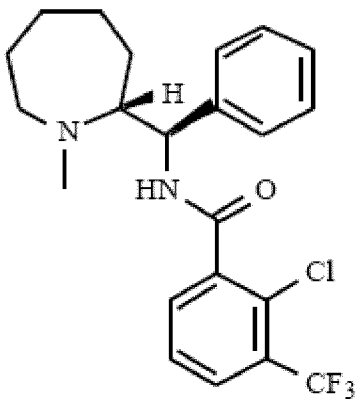

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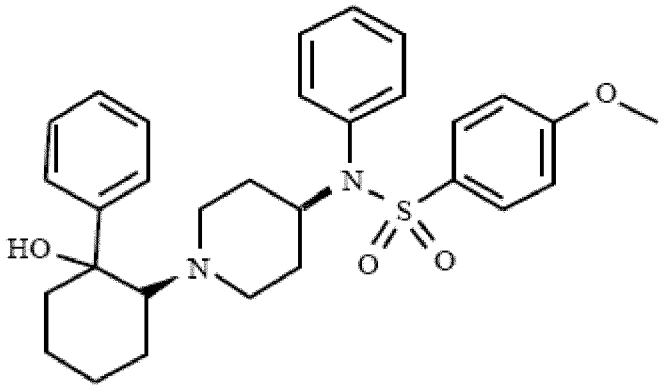

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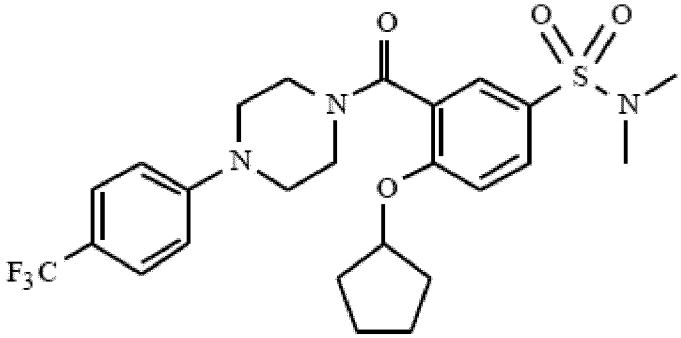

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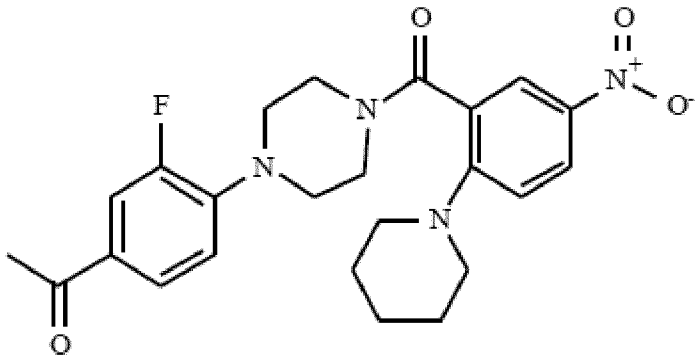

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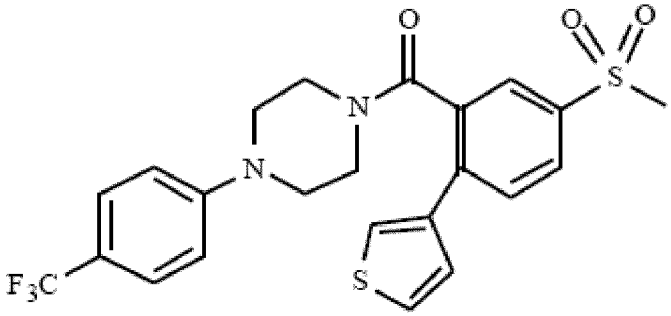

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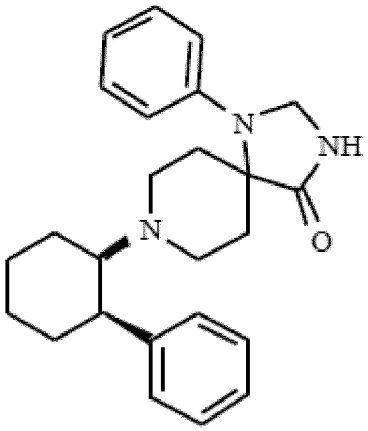

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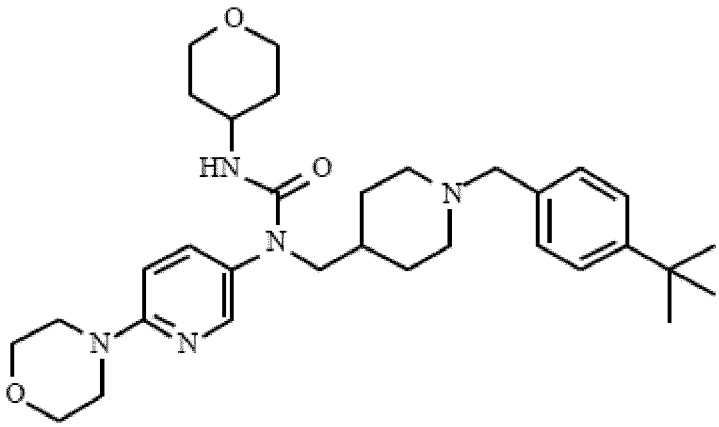

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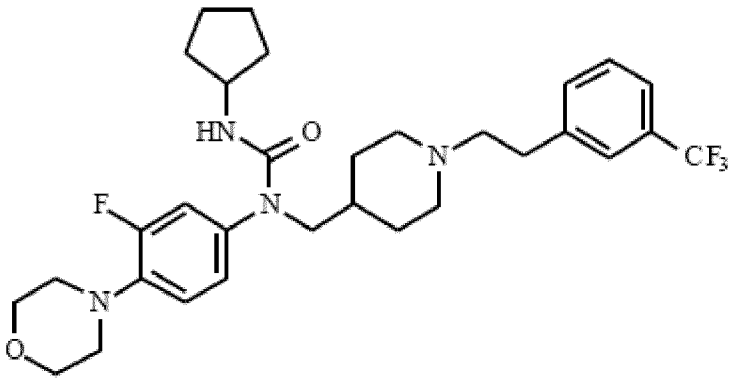

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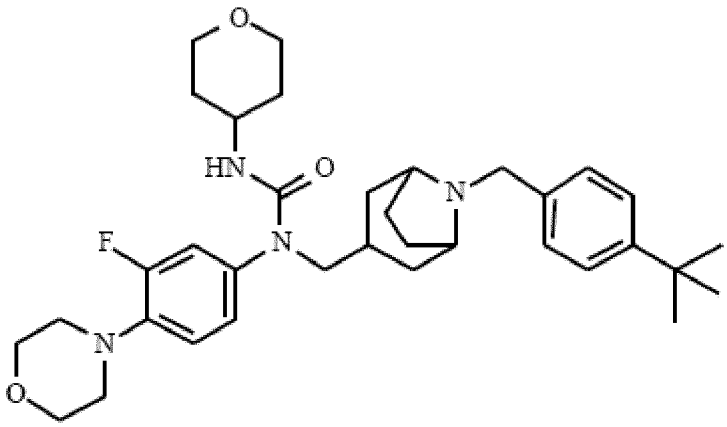

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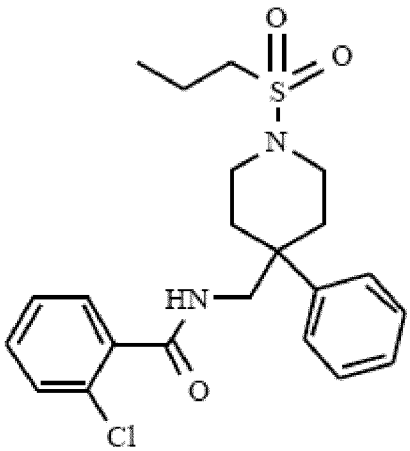

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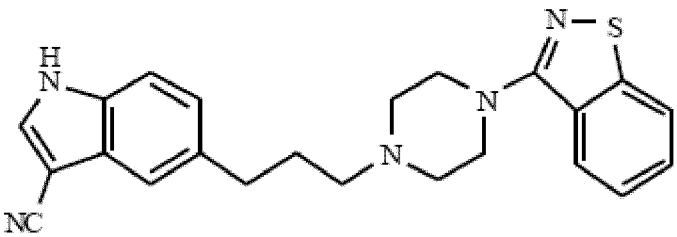

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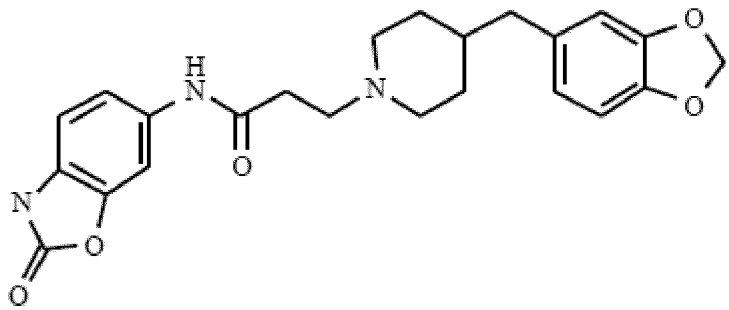

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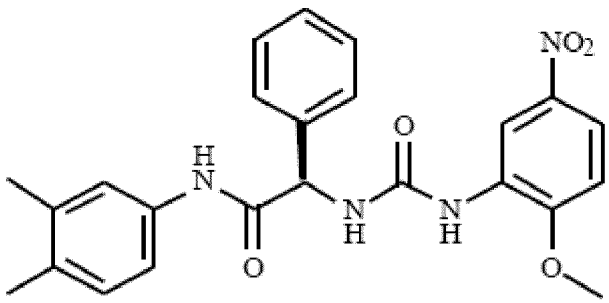


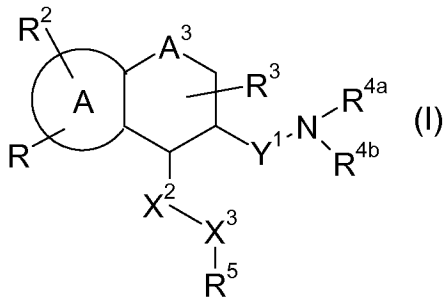
WO 2004022528

(see also Hashimoto K., Recent Patents on CNS Drug Discovery, 2006, 1, 43–53; Harsing L.G. et al., Current Medicinal Chemistry, 2006, 13, 1017–1044; Javitt D.C., Molecular Psychiatry (2004) 9, 984–997; Lindsley, C.W. et al., Current Topics in Medicinal Chemistry, 2006, 6, 771–785; Lindsley C.W. et al., Current Topics in Medicinal Chemistry, 2006, 6, 1883–1896).

It was one object of the present invention to provide further glycine transporter inhibitors.

Summary of the Invention

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



(I)

wherein

A is a 5- or 6-membered ring;

R is R^1-W-A^1-Q-Y-A^2-X^1-;

R^1 is hydrogen, alkyl, cycloalkylalkyl, halogenated alkyl, trialkylsilylalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkylcarbonylaminoalkyl, alkyloxycarbonylaminoalkyl, alkylaminocarbonylaminoalkyl, dialkylaminocarbonylaminoalkyl, alkylsulfonylaminoalkyl, (optionally substituted arylalkyl) aminoalkyl, op-

tionally substituted arylalkyl, optionally substituted heterocyclylalkyl, cycloalkyl, alkylcarbonyl, alkoxycarbonyl, halogenated alkoxycarbonyl, aryloxycarbonyl, aminocarbonyl, alkylaminocarbonyl, (halogenated alkyl)aminocarbonyl, arylaminocarbonyl, alkenyl, alkynyl, optionally substituted aryl, hydroxy, alkoxy, halogenated alkoxy, hydroxyalkoxy, alkoxyalkoxy, aminoalkoxy, alkylaminoalkoxy, dialkylaminoalkoxy, alkylcarbonylaminoalkoxy, arylcarbonylaminoalkoxy, alkoxycarbonylaminoalkoxy, arylalkoxy, alkylsulfonylaminoalkoxy, (halogenated alkyl)sulfonylaminoalkoxy, arylsulfonylaminoalkoxy, (arylalkyl)sulfonylaminoalkoxy, heterocyclylsulfonylaminoalkoxy, heterocyclylalkoxy, aryloxy, heterocyclyloxy, alkylthio, halogenated alkylthio, alkylamino, (halogenated alkyl)amino, dialkylamino, di-(halogenated alkyl)amino, alkylcarbonylamino, (halogenated alkyl)carbonylamino, arylcarbonylamino, alkylsulfonylamino, (halogenated alkyl)sulfonylamino, arylsulfonylamino or optionally substituted heterocyclyl;

W is $-NR^8-$ or a bond;

A^1 is optionally substituted alkylene or a bond;

Q is $-S(O)_2-$ or -C(O)-;

Y is $-NR^9-$ or a bond;

A^2 is optionally substituted alkylene, alkylene-CO-, -CO-alkylene, alkylene-O-alkylene, alkylene-NR^{10}-alkylene, optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted arylene, optionally substituted heteroarylene or a bond;

X^1 is -O-, $-NR^{11}-$, -S-, optionally substituted alkylene, optionally substituted alkenylen, optionally substituted alkynylene;

A^3 is -O-, -S- or $-NR^{16}-$;

R^2 is hydrogen, halogen, alkyl, halogenated alkyl, hydroxyalkyl, -CN, alkenyl, alkynyl, optionally substituted aryl, hydroxy, alkoxy, halogenated alkoxy, alkoxycarbonyl, alkenyloxy, arylalkoxy, alkylcarbonyloxy, alkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, amino, alkylamino, 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;

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^{4a} is hydrogen, alkyl, cycloalkylalkyl, halogenated alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, CH_2CN, aralkyl, cycloalkyl,-CHO, alkylcarbonyl, (halogenated alkyl)carbonyl, arylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, alkenyl, $-C(=NH)NH_2$, -C(=NH)NHCN, alkylsulfonyl, arylsulfonyl, amino, -NO or heterocyclyl; or

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

R^{4b} is hydrogen, alkyl, halogenated alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, CH_2CN, -CHO, alkylcarbonyl, (halogenated alkyl)carbonyl, arylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, alkenyl, $-C(=NH)NH_2$, -C(=NH)NHCN, alkylsulfonyl, arylsulfonyl, amino, -NO or heterocyclyl; or

R^{4a}, R^{4b} together are optionally substituted alkylene, wherein one $-CH_2-$ of alkylene may be replaced by an oxygen atom or $-NR^{17}$;

X^2 is -O-, $-NR^6$-, -S-, $>CR^{12a}R^{12b}$ or a bond;

X^3 is -O-, $-NR^7$-, -S-, $>CR^{13a}R^{13b}$ or a bond;

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

R^6 is hydrogen or alkyl;

R^7 is hydrogen or alkyl;

R^8 is hydrogen or alkyl;

R^9 is hydrogen, alkyl, cycloalkyl, aminoalkyl, optionally substituted arylalkyl or heterocyclyl; or

R^9, R^1 together are alkylene; or

R^9 is alkylene that is bound to a carbon atom in A^2 and A^2 is alkylene or to a carbon atom in X^1 and X^1 is alkylene;

R^{10} is hydrogen, alkyl or alkylsulfonyl;

R^{11} is hydrogen or alkyl, or

R^9, R^{11}
together are alkylene,

R^{12a} is hydrogen, optionally substituted alkyl, alkylaminoalkyl, dialkylaminoalkyl, heterocyclylalkyl, optionally substituted aryl or hydroxy;

R^{12b} is hydrogen or alkyl, or

R^{12a}, R^{12b}
together are carbonyl or optionally substituted alkylene, wherein one $-CH_2-$ of alkylene may be replaced by an oxygen atom or $-NR^{14}-$;

R^{13a} is hydrogen, optionally substituted alkyl, alkylaminoalkyl, dialkylaminoalkyl, heterocyclylalkyl, optionally substituted aryl or hydroxy;

R^{13b} is hydrogen or alkyl, or

R^{13a}, R^{13b}
together are carbonyl or optionally substituted alkylene, wherein one $-CH_2-$ of alkylene may be replaced by an oxygen atom or $-NR^{15}-$;

R^{14} is hydrogen or alkyl;

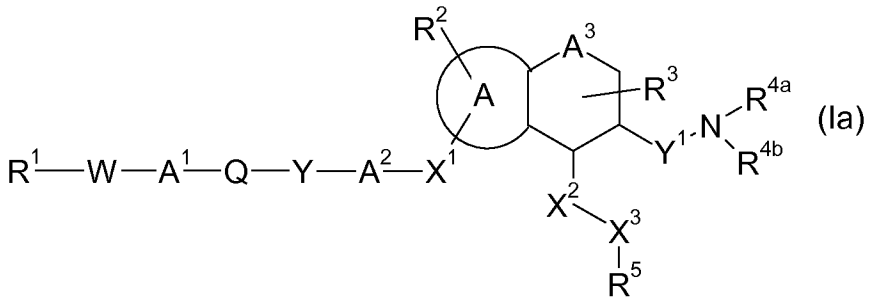
R^{15} is hydrogen or alkyl;

R^{16} is hydrogen, alkyl, cycloalkylalkyl, halogenated alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, CH_2CN, arylalkyl, cycloalkyl, -CHO, alkylcarbonyl, (halogenated alkyl)carbonyl, arylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, alkenyl, $-C(=NH)NH_2$, -C(=NH)NHCN, alkylsulfonyl, arylsulfonyl, amino, -NO or heterocyclyl; and

R^{17} is hydrogen or alkyl,

or a physiologically tolerated salt thereof.

Thus, the present invention relates to aminochromane, aminothiochromane and amino-1,2,3,4-tetrahydroquinoline derivatives having the formula (Ia)



(Ia)

wherein A, R^1, W, A^1, Q, Y, A^2, X^1, R^2, A^3, R^3, Y^1, R^{4a}, R^{4b}, X^2, X^3, R^5 are as defined herein.

Thus, the terms aminochromane, aminothiochromane and amino-1,2,3,4-tetrahydroquinoline derivative are used herein to denote in particular aminochromanes (A^3 is -O-), thiochromanes (A^3 is -S-) and 1,2,3,4-tetrahydroquinolines (A^3 is -NR^{16}-) as well as fused tetrahydropyranes, tetrahydrothiopyranes 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. The compounds of formula (I) may exhibit favorable efflux properties which may lead to enhanced oral bioavailability and/or increased brain availability.

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.

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.

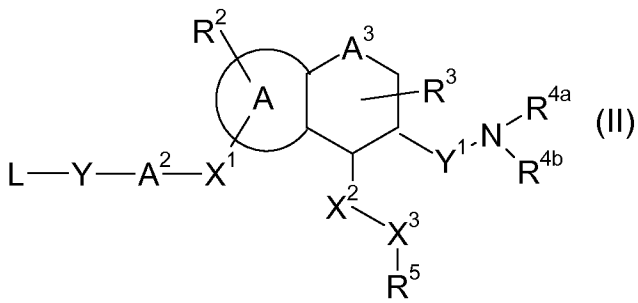
Glycine transport inhibitors and in particular inhibitors of the glycine transporter GlyT1 are known to be useful in treating a variety of neurologic and psychiatric disorders.

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.

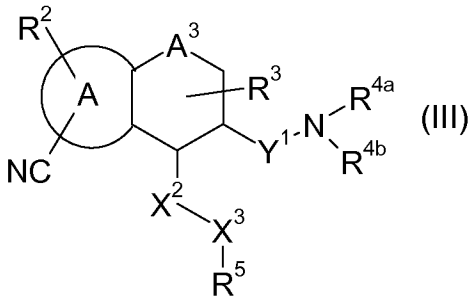
The present invention also relates to the use of the compounds of formula (I) in the manufacture of a medicament for treating a neurologic or psychiatric disorder and corresponding methods of treating said disorders. The present invention also relates to the use of the compounds of formula (I) in the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

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



wherein L is an amino-protecting group, Y is NR^9, and A^2, X^1, A, R^2, A^3, R^3, Y^1, R^{4a}, R^{4b}, X^2, X^3, R^5 and R^9 are defined as herein.

Further, the present invention relates to aminochromane, aminothiochromane and amino-1,2,3,4-tetrahydroquinoline derivatives of formula (I) wherein R is –CN, i.e. aminochromane, aminothiochromane and amino-1,2,3,4-tetrahydroquinoline derivatives having the formula (III)



(III)

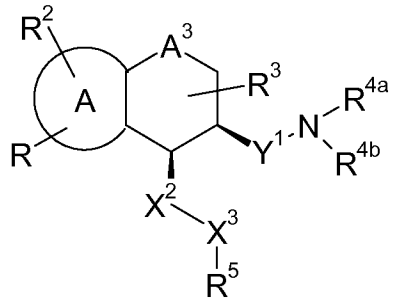
wherein A, R^2, A^3, R^3, Y^1, R^{4a}, R^{4b}, X^2, X^3, R^5 are as defined herein.

The aminochromane, aminothiochromane and amino-1,2,3,4-tetrahydroquinoline derivatives of formula (II) or formula (III) are useful as intermediates in the preparation of GlyT1 inhibitors, in particular those of formula (I).

Detailed Description Of The Invention

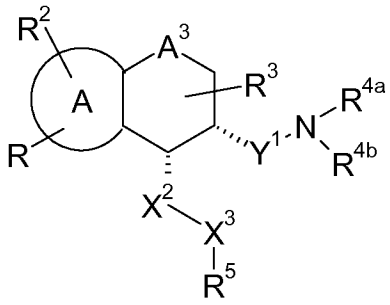
Provided that the aminochromane, aminothiochromane and amino-1,2,3,4-tetrahydroquinoline derivatives of the formula (I), (II) or (III) of a given constitution may exist in different spatial arrangements, for example if they possess one or more centers of asymmetry, polysubstituted rings or double bonds, 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), (II) or (III) and/or of their salts.

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



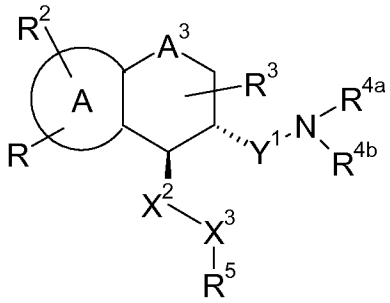
wherein A, R, R^2, A^3, R^3, Y^1, R^{4a}, R^{4b}, X^2, X^3, R^5 are as defined herein.

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



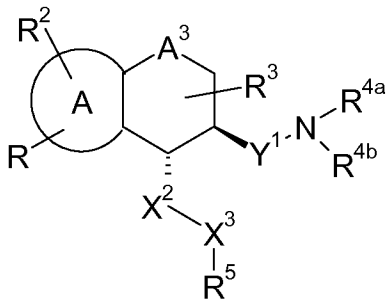
wherein A, R, R^2, A^3, R^3, Y^1, R^{4a}, R^{4b}, X^2, X^3, R^5 are as defined herein.

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



wherein A, R, R^2, A^3, 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 A, R, R^2, A^3, 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, aminothiochromane and amino-1,2,3,4-tetrahydroquinoline derivatives of the formula (I), (II) or (III) 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, C_1-C_4-alkylsulfonic acids, such as methanesulfonic acid, cycloaliphatic sulfonic acids, such as S-(+)-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 Fortschritte der Arzneimittelforschung [Advances in drug research], Volume 10, pages 224 ff., Birkhäuser Verlag, Basel and Stuttgart, 1966. The physiologically tolerated salts of the aminochromane, aminothiochromane and amino-1,2,3,4-tetrahydroquinoline derivatives also include salts of a physiologically tolerated anion with aminochromane, aminothiochromane 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), (II) or (III) as defined herein, wherein at least one of the atoms has been replaced by its stable, non-radioactive isotope (e.g., hydrogen by deuterium, ^{12}C by ^{13}C, ^{14}N by ^{15}N, ^{16}O by ^{18}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), (II) or (III).

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; Schwarcz 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; MacLennan A H et al. Am. J. Obstet Gynecol. 1981 139: 948). Thus, it is clear that any deuterium released, for instance, during 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; Czakja 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 D_2SO_4/D_2O. 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 and 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 WO1997010223, WO2005099353, WO1995007271, WO2006008754; US Patent Nos. 7538189; 7534814; 7531685; 7528131; 7521421; 7514068; 7511013; and US Patent Application Publication Nos. 20090137457; 20090131485; 20090131363; 20090118238; 20090111840; 20090105338; 20090105307; 20090105147; 20090093422; 20090088416; 20090082471, the methods are hereby incorporated by reference.

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_n-C_m indicates in each case the possible number of carbon atoms in the group.

Unless indicated otherwise, the term "substituted" means that a radical is substituted with 1, 2 or 3, especially 1, substituent which are in particular selected from the group consisting of halogen, C_1-C_4-alkyl, hydroxy-C_1-C_4-alkyl, C_3-C_{12}-heterocyclyl-alkyl, C_1-C_4-alkoxy-

C_1-C_4-alkyl, amino-C_1-C_4-alkyl, C_1-C_4-alkenyl, oxo (=O), OH, SH, CN, CF_3, O-CF_3, COOH, O-CH_2-COOH, C_1-C_6-alkoxy, C_1-C_6-alkylthio, C_3-C_7-cycloalkyl, COO-C_1-C_6-alkyl, $CONH_2$, CONH-C_1-C_6-alkyl, SO_2NH-C_1-C_6-alkyl, CON-(C_1-C_6-alkyl)$_2$, SO_2N-(C_1-C_6-alkyl)$_2$, NH_2, NH-C_1-C_6-alkyl, N-(C_1-C_6-alkyl)$_2$, NH-(C_1-C_4-alkyl- C_6-C_{12}-aryl), NH-CO-C_1-C_6-alkyl, NH-SO_2-C_1-C_6-alkyl, SO_2-C_1-C_6-alkyl, C_6-C_{12}-aryl, O-C_6-C_{12}-aryl, O-CH_2-C_6-C_{12}-aryl, CONH-C_6-C_{12}-aryl, SO_2NH-C_6-C_{12}-aryl, CONH-C_3-C_{12}-heterocyclyl, SO_2NH-C_3-C_{12}-heterocyclyl, SO_2-C_6-C_{12}-aryl, NH-SO_2-C_6-C_{12}-aryl, NH-CO-C_6-C_{12}-aryl, NH-SO_2-C_3-C_{12}-heterocyclyl, NH-CO-C_3-C_{12}-heterocyclyl and C_3-C_{12}-heterocyclyl, wherein aryl and heterocyclyl in turn may be unsubstituted or substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy and C_1-C_4-haloalkoxy.

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

C_1-C_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-C_4-alkyl such as ethyl, n-propyl, iso-propyl, n-butyl, 2-butyl, iso-butyl or tert-butyl. C_1-C_2-Alkyl is methyl or ethyl, C_1-C_3-alkyl is additionally n-propyl or isopropyl.

C_1-C_6-Alkyl is a straight-chain or branched alkyl group having from 1 to 6 carbon atoms. Examples include methyl, C_2-C_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 C_1-C_4-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 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-(dihalogenomethyl)-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 C_1-C_4 alkyl groups as defined, such as trifluoromethyl.

C_6-C_{12}-Aryl-C_1-C_4-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 C_6-C_{12}-aryl, such as in benzyl.

Hydroxy-C_1-C_4-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.

C_1-C_6-Alkoxy-C_1-C_4-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, ethoxymethyl, (R)-1-ethoxyethyl, (S)-1-ethoxyethyl, 2-ethoxyethyl, (R)-1-ethoxypropyl, (S)-1-ethoxypropyl, 2-ethoxypropyl, 3-ethoxypropyl, (R)-2-ethoxy-1-methylethyl, (S)-2-ethoxy-1-methylethyl, 2-ethoxy-1-(ethoxymethyl)ethyl, (R)-1-ethoxybutyl, (S)-1-ethoxybutyl, 2-ethoxybutyl, 3-ethoxybutyl, 4-ethoxybutyl.

Amino-C_1-C_4-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.

C_1-C_6-Alkylamino-C_1-C_4-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 C_1-C_6-alkylamino group, in particular by a C_1-C_4-alkylamino group, such as in methylaminomethyl, ethylaminomethyl, n-propylaminomethyl, iso-propylaminomethyl, n-butylaminomethyl, 2-butylaminomethyl, iso-butylaminomethyl or tert-butylaminomethyl.

Di-C_1-C_6-Alkylamino-C_1-C_4-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-C_1-C_6-Alkylamino group, in particular by a di-C_1-C_4-alkylamino group, such as in dimethylaminomethyl.

C_1-C_6-Alkylcarbonylamino-C_1-C_4-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 C_1-C_6-alkylcarbonylamino group, in particular by a C_1-C_4-alkylcarbonylamino group, such as in methylcarbonylaminomethyl, ethylcarbonylaminomethyl, n-propylcarbonylaminomethyl, iso-propylcarbonylaminomethyl, n-butylcarbonylaminomethyl, 2-butylcarbonylaminomethyl, iso-butylcarbonylaminomethyl or tert-butylcarbonylaminomethyl.

C_1-C_6-Alkylaminocarbonylamino-C_1-C_4-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 C_1-C_6-alkylaminocarbonylamino group, in particular by a C_1-C_4-alkylaminocarbonylamino group, such as in methylaminocarbonylaminomethyl, ethylaminocarbonylaminomethyl, n-propylaminocarbonylaminomethyl, iso-propylaminocarbonylaminomethyl, n-butylaminocarbonylaminomethyl, 2-butylaminocarbonylaminomethyl, iso-butylaminocarbonylaminomethyl or tert-butylaminocarbonylaminomethyl.

Di-C_1-C_6-alkylaminocarbonylamino-C_1-C_4-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-C_1-C_6-alkylaminocarbonylamino group, in particular by a di-C_1-C_4-alkylaminocarbonylamino group, such as in dimethylaminocarbonylaminomethyl, dimethylaminocarbonylaminoethyl, dimethylaminocarbonylaminon-propyl.

C_1-C_6-Alkylsulfonylamino-C_1-C_4-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 C_1-C_6-alkylsulfonylamino group, in particular by a C_1-C_4-alkylsulfonylamino group, such as in methylsulfonylaminomethyl, ethylsulfonylaminomethyl, n-propylsulfonylaminomethyl, iso-propylsulfonylaminomethyl, n-butylsulfonylaminomethyl, 2-butylsulfonylaminomethyl, iso-butylsulfonylaminomethyl or tert-butylsulfonylaminomethyl.

(C_6-C_{12}-Aryl-C_1-C_6-alkyl)amino-C_1-C_4 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 (C_6-C_{12}-aryl-C_1-C_6-alkyl)amino group, in particular a (C_6-C_{12}-aryl-C_1-C_2-alkyl)amino group, such as in benzylaminomethyl.

C_3-C_{12}-Heterocyclyl-C_1-C_4-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 C_3-C_{12}-heterocyclyl, such as in N-pyrrolidinylmethyl, N-piperidinylmethyl, N-morpholinylmethyl.

C_3-C_{12}-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 C_1-C_4 alkyl radicals, preferably one or more methyl radicals.

Carbonyl is >C=O.

C_1-C_6-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.

Halogenated C_1-C_6-alkylcarbonyl is C_1-C_6-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 fluoromethylcarbonyl, difluoromethylcarbonyl, trifluoromethylcarbonyl. Further examples are 1,1,1-trifluoroeth-2-ylcarbonyl, 1,1,1-trifluoroprop-3-ylcarbonyl.

C_6-C_{12}-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 benzoyl.

C_1-C_6-Alkoxycarbonyl 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 C_1-C_6-alkoxycarbonyl is a C_1-C_6-alkoxycarbonyl 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.

C_6-C_{12}-Aryloxycarbonyl 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 phenoxycarbonyl.

Cyano is -C≡N.

Aminocarbonyl is $NH_2C(O)$-.

C_1-C_6-Alkylaminocarbonyl is a radical of the formula R-NH-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 methylaminocarbonyl.

(Halogenated C_1-C_4-alkyl)aminocarbonyl is a C_1-C_4-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.

C_6-C_{12}-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.

C_2-C_6-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. C_3-C_5-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.

C_2-C_6-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. C_3-C_5-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.

C_1-C_4-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.

C_2-C_4-Alkenylene is straight-chain or branched alkenylene group having from 2 to 4 carbon atoms.

C_2-C_4-Alkynylene is straight-chain or branched alkynylene group having from 2 to 4 carbon atoms. Examples include propynylene.

C_6-C_{12}-Aryl is a 6- to 12-membered, in particular 6- to 10-membered, aromatic cyclic radical. Examples include phenyl and naphthyl.

C_3-C_{12}-Arylene is an aryl diradical. Examples include phen-1,4-ylene and phen-1,3-ylene.

Hydroxy is –OH.

C_1-C_6-Alkoxy 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, isopropoxy, 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-methylpropoxy and 1-ethyl-2-methylpropoxy.

Halogenated C_1-C_6-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-1-methylethoxy, (S)-2-halogeno-1-methylethoxy, (R)-2,2-dihalogeno-1-methylethoxy, (S)-2,2-dihalogeno-1-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-1-(halogenomethyl)ethoxy, 1-(dihalogenomethyl)-2,2-dihalogenoethoxy, (R)-1-halogenobutoxy, (S)-1-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 C_1-C_4 alkoxy groups as defined, such as trifluoromethoxy.

C_1-C_6-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-C_6-Alkoxy-C_1-C_4-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, eth-

oxymethoxy, 2-ethoxyethoxy, 1-ethoxyethoxy, 3-ethoxypropoxy, 2-ethoxypropoxy, 1-methyl-1-ethoxyethoxy and the like.

Amino-C_1-C_4-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-C_6-Alkylamino-C_1-C_4-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 methylaminomethoxy, 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-butylamino)ethoxy, 2-(iso-butylamino)ethoxy, 2-(tert-butylamino)ethoxy.

Di-C_1-C_6-alkylamino-C_1-C_4-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-ethylamino)ethoxy, 2-(dimethylamino)ethoxy, 2-(diethylamino)ethoxy, 2-(N-methyl-N-ethylamino)ethoxy.

C_1-C_6-Alkylcarbonylamino-C_1-C_4-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, n-butylcarbonylaminomethoxy, 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-butylcarbonylamino)ethoxy, 2-(iso-butylcarbonylamino)ethoxy, 2-(tert-butylcarbonylamino)ethoxy.

C_6-C_{12}-Arylcarbonylamino-C_1-C_4-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 C_6-C_{12}-arylcarbonylamino group as defined herein. Examples include 2-(benzoylamino)ethoxy.

C_1-C_6-Alkoxycarbonylamino-C_1-C_4-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 alkoxycarbonylamino group wherein the alkoxy group has from 1 to 6, 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.

C_2-C_6-Alkenyloxy is a radical of the formula R-O-, 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. C_3-C_5-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.

C_6-C_{12}-Aryl-C_1-C_4-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 C_6-C_{12}-aryl group as defined herein. Examples include benzyloxy.

C_1-C_6-Alkylsulfonylamino-C_1-C_4-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 C_1-C_6-alkyl)sulfonylamino-C_1-C_4-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.

C_6-C_{12}-Arylsulfonylamino-C_1-C_4-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 C_6-C_{12}-arylsulfonylamino group as defined herein. Examples include 2-(phenylsulfonylamino)ethoxy, 2-(naphthylsulfonylamino)ethoxy.

(C_6-C_{12}-Aryl-C_1-C_6-alkyl)sulfonylamino-C_1-C_4-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 (C_6-C_{12}-aryl-C_1-C_6-alkyl)sulfonylamino group, preferably by a (C_6-C_{12}-aryl-C_1-C_2-alkyl)sulfonylamino group. Examples include 2-(benzylsulfonylamino)ethoxy.

C_3-C_{12}-Heterocyclylsulfonylamino-C_1-C_4-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 C_3-C_{12}-heterocyclylsulfonylamino group as defined herein. Examples include 2-(pyridin-3-yl-sulfonylamino)ethoxy.

C_3-C_{12}-Heterocyclyl-C_1-C_4-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 C_3-C_{12}-heterocyclyl group as defined herein. Examples include 2-(N-pyrrolidinyl)ethoxy, 2-(N-morpholinyl)ethoxy and 2-(N-imidazolyl)ethoxy.

C_1-C_2-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.

C_6-C_{12}-Aryloxy is a radical of the formula R-O-, wherein R is an aryl group having from 6 to 12, in particular 6 carbon atoms as defined herein. Examples include phenoxy.

C_3-C_{12}-Heterocyclyloxy is a radical of the formula R-O-, wherein R is a C_3-C_{12}-heterocyclyl group having from 3 to 12, in particular from 3 to 7 carbon atoms as defined herein. Examples include pyridin-2-yloxy.

C_1-C_6-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 C_1-C_6-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-halogenopropylthio, 3-halogenopropylthio, 1,1-dihalogenopropylthio, 2,2-dihalogenopropylthio, 3,3-dihalogenopropylthio, 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 C_1-C_4 alkylthio groups as defined, such as trifluoromethylthio.

C_1-C_6-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-methylpropyl.

C_1-C_6-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-methylpropyl.

(Halogenated C_1-C_6-alkyl)sulfonyl is a C_1-C_6-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.

C_6-C_{12}-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.

(C_6-C_{12}-Aryl-C_1-C_4-alkyl)sulfonyl is a radical of the formula R-S(O)$_2$-, wherein R is a C_6-C_{12}-aryl-C_1-C_4-alkyl radical, in particular a C_6-C_{12}-aryl-C_1-C_2-alkyl radical as defined herein. Examples include benzylsulfonyl.

C_3-C_{12}-Heterocyclylsulfonyl is a radical of the formula R-S(O)$_2$-, wherein R is C_3-C_{12}-heterocyclyl as defined herein.

Aminosulfonyl is NH_2-S(O)$_2$-.

C_1-C_6-Alkylaminosulfonyl is a radical of the formula R-NH-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 methylaminosulfonyl, ethylaminosulfonyl, n-propylaminosulfonyl, iso-propylaminosulfonyl, n-butylaminosulfonyl, 2-butylaminosulfonyl, iso-butylaminosulfonyl, tert-butylaminosulfonyl.

Di-C_1-C_6-alkylaminosulfonyl is a radical of the formula RR'N-S(O)$_2$- 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.

C_6-C_{12}-Arylaminosulfonyl is a radical of the formula R-NH-S(O)$_2$- wherein R is an aryl radical having from 6 to 12, preferably 6 carbon atoms as defined herein.

Amino is NH_2.

C_1-C_6-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.

(Halogenated C_1-C_6-alkyl)amino is a C_1-C_6-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-C_1-C_6-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 C_1-C_6-alkyl)amino is a di-C_1-C_6-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.

C_1-C_6-Alkylcarbonylamino is a radical of the formula R-C(O)-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-butyramido, 2-methylpropionamido (isopropylcarbonylamino), 2,2-dimethylpropionamido and the like.

(Halogenated C_1-C_6-alkyl)carbonylamino is a C_1-C_6-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.

C_6-C_{12}-Arylcarbonylamino is a radical of the formula R-C(O)-NH-, wherein R is an aryl radical having from 6 to 12 carbon atoms as defined herein. Examples include phenylcarbonylamino.

C_2-C_6-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. C_3-C_5-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.

C_1-C_6-Alkylsulfonylamino is a radical of the formula R-S(O)$_2$-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, isopropylsulfonylamino, n-butylsulfonylamino, 2-butylsulfonylamino, iso-butylsulfonylamino, tert-butylsulfonylamino.

(Halogenated C_1-C_6 alkyl)sulfonylamino is a C_1-C_6-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.

C_6-C_{12}-Arylsulfonylamino is a radical of the formula R-S(O)$_2$-NH-, wherein R is an aryl radical having from 6 to 12 carbon atoms as defined herein. Examples include phenylsulfonylamino.

Nitro is -NO_2.

C_3-C_{12}-Heterocyclyl 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 C_3-C_{12}-heterocyclyl include:

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

C-bound, 5-membered, saturated rings, such as
tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-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, tetrahydroisothiazol-3-yl, tetrahydroisothiazol-4-yl, tetrahydroisothiazol-5-yl, 1,2-dithiolan-3-yl, 1,2-dithiolan-4-yl, tetrahydroimidazol-2-yl, tetrahydroimidazol-4-yl, tetrahydrooxazol-2-yl, tetrahydrooxazol-4-yl, tetrahydrooxazol-5-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, 1,3,2-dioxathiolan-4-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-oxathian-2-yl, 1,3-oxathian-4-yl, 1,3-oxathian-5-yl, 1,3-oxathian-6-yl, 1,4-oxathian-2-yl, 1,4-oxathian-3-yl, 1,2-dithian-3-yl, 1,2-dithian-4-yl, hexahydropyrimidin-2-yl, hexahydropyrimidin-4-yl, hexahydropyrimidin-5-yl, hexahydropyrazin-2-yl, hexahydropyridazin-3-yl, hexahydropyridazin-4-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-oxazin-2-yl, tetrahydro-1,4-oxazin-3-yl, tetrahydro-1,2-oxazin-3-yl, tetrahydro-1,2-oxazin-4-yl, tetrahydro-1,2-oxazin-5-yl, tetrahydro-1,2-oxazin-6-yl;

N-bound, 5-membered, saturated rings, such as
tetrahydropyrrol-1-yl (pyrrolidin-1-yl), tetrahydropyrazol-1-yl, tetrahydroisoxazol-2-yl, tetrahydroisothiazol-2-yl, tetrahydroimidazol-1-yl, tetrahydrooxazol-3-yl, tetrahydrothiazol-3-yl;

N-bound, 6-membered, saturated rings, such as
piperidin-1-yl, hexahydropyrimidin-1-yl, hexahydropyrazin-1-yl (piperazin-1-yl), hexahydropyridazin-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-di-hydrofuran-3-yl, 4,5-dihydrofuran-2-yl, 4,5-dihydrofuran-3-yl, 2,3-dihydro-thien-2-yl, 2,3-dihydrothien-3-yl, 2,5-dihydrothien-2-yl, 2,5-dihydrothien-3-yl, 4,5-dihydrothien-2-yl, 4,5-dihydrothien-3-yl, 2,3-dihydro-1H-pyrrol-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, 3,4-dihydro-2H-pyrrol-2-yl, 3,4-dihydro-2H-pyrrol-3-yl, 3,4-dihydro-5H-pyrrol-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-pyrazol-3-yl, 2,5-dihydro-1H-pyrazol-4-yl, 2,5-dihydro-1H-pyrazol-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-dihydro-1H-imidazol-2-yl, 4,5-dihydro-1H-imidazol-4-yl, 4,5-dihydro-1H-imidazol-5-yl, 2,5-dihydro-1H-imidazol-2-yl, 2,5-dihydro-1H-imidazol-4-yl, 2,5-dihydro-1H-imidazol-5-yl, 2,3-dihydro-1H-imidazol-2-yl, 2,3-dihydro-1H-imidazol-4-yl, 4,5-dihydro-oxazol-2-yl, 4,5-dihydrooxazol-4-yl, 4,5-dihydrooxazol-5-yl, 2,5-dihydrooxazol-2-yl, 2,5-dihydrooxazol-4-yl, 2,5-dihydrooxazol-5-yl, 2,3-dihydrooxazol-2-yl, 2,3-dihydrooxazol-4-yl, 2,3-dihydrooxazol-5-yl, 4,5-dihydrothiazol-2-yl, 4,5-dihydrothiazol-4-yl, 4,5-dihydrothiazol-5-yl, 2,5-dihydrothiazol-2-yl, 2,5-dihydrothiazol-4-yl, 2,5-dihydrothiazol-5-yl, 2,3-dihydrothiazol-2-yl, 2,3-dihydrothiazol-4-yl, 2,3-dihydrothiazol-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;

C-bound, 6-membered, partially unsaturated rings, such as
2H-3,4-dihydropyran-6-yl, 2H-3,4-dihydropyran-5-yl, 2H-3,4-dihydropyran-4-yl, 2H-3,4-dihydropyran-3-yl, 2H-3,4-dihydropyran-2-yl, 2H-3,4-dihydrothiopyran-6-yl, 2H-3,4-dihydrothiopyran-5-yl, 2H-3,4-dihydrothiopyran-4-yl, 2H-3,4-dihydrothiopyran-3-yl, 2H-3,4-dihydrothiopyran-2-yl, 1,2,3,4-tetrahydropyridin-6-yl, 1,2,3,4-tetrahydropyridin-5-yl, 1,2,3,4-tetrahydropyridin-4-yl, 1,2,3,4-tetra-hydropyridin-3-yl, 1,2,3,4-tetrahydropyridin-2-

yl, 2H-5,6-dihydropyran-2-yl, 2H-5,6-dihydropyran-3-yl, 2H-5,6-dihydropyran-4-yl, 2H-5,6-dihydropyran-5-yl, 2H-5,6-dihydropyran-6-yl, 2H-5,6-dihydrothiopyran-2-yl, 2H-5,6-dihydrothiopyran-3-yl, 2H-5,6-dihydrothiopyran-4-yl, 2H-5,6-dihydrothiopyran-5-yl, 2H-5,6-dihydrothiopyran-6-yl, 1,2,5,6-tetrahydropyridin-2-yl, 1,2,5,6-tetrahydropyridin-3-yl, 1,2,5,6-tetrahydropyridin-4-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,5,6-tetrahydropyridin-6-yl, 2,3,4,5-tetrahydropyridin-2-yl, 2,3,4,5-tetrahydropyridin-3-yl, 2,3,4,5-tetrahydropyridin-4-yl, 2,3,4,5-tetrahydropyridin-5-yl, 2,3,4,5-tetrahydropyridin-6-yl, 4H-pyran-2-yl, 4H-pyran-3-yl-, 4H-pyran-4-yl, 4H-thiopyran-2-yl, 4H-thiopyran-3-yl, 4H-thiopyran-4-yl, 1,4-dihydropyridin-2-yl, 1,4-dihydropyridin-3-yl, 1,4-dihydropyridin-4-yl, 2H-pyran-2-yl, 2H-pyran-3-yl, 2H-pyran-4-yl, 2H-pyran-5-yl, 2H-pyran-6-yl, 2H-thiopyran-2-yl, 2H-thiopyran-3-yl, 2H-thiopyran-4-yl, 2H-thiopyran-5-yl, 2H-thiopyran-6-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydro-pyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydro-pyridin-6-yl, 3,4-dihydropyridin-2-yl, 3,4-dihydropyridin-3-yl, 3,4-dihydro-pyridin-4-yl, 3,4-dihydropyridin-5-yl, 3,4-dihydropyridin-6-yl, 2,5-dihydropyridin-2-yl, 2,5-dihydropyridin-3-yl, 2,5-dihydropyridin-4-yl, 2,5-dihydropyridin-5-yl, 2,5-dihydropyridin-6-yl, 2,3-dihydropyridin-2-yl, 2,3-dihydropyridin-3-yl, 2,3-dihydropyridin-4-yl, 2,3-dihydropyridin-5-yl, 2,3-dihydropyridin-6-yl, 2H-5,6-dihydro-1,2-oxazin-3-yl, 2H-5,6-dihydro-1,2-oxazin-4-yl, 2H-5,6-dihydro-1,2-oxazin-5-yl, 2H-5,6-dihydro-1,2-oxazin-6-yl, 2H-5,6-dihydro-1,2-thiazin-3-yl, 2H-5,6-dihydro-1,2-thiazin-4-yl, 2H-5,6-dihydro-1,2-thiazin-5-yl, 2H-5,6-dihydro-1,2-thiazin-6-yl, 4H-5,6-dihydro-1,2-oxazin-3-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-3-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-3-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-3-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-3-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-3-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-tetra-hydropyridazin-5-yl, 1,2,5,6-tetrahydropyridazin-6-yl, 1,2,3,6-tetrahydro-pyridazin-3-yl, 1,2,3,6-tetrahydropyridazin-4-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-oxazin-5-yl, 4H-5,6-dihydro-1,3-oxazin-6-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-tetrahydropyrazin-2-yl, 1,2,3,4-tetrahydropyrazin-5-yl, 1,2,3,4-tetrahydro-pyrimidin-2-yl, 1,2,3,4-tetrahydropyrimidin-4-yl, 1,2,3,4-tetrahydropyrimidin-5-yl, 1,2,3,4-tetrahydropyrimidin-6-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-oxazin-4-yl, 6H-1,3-oxazin-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-thiazin-2-yl, 4H-1,4-thiazin-3-yl, 1,4-dihydropyridazin-3-yl, 1,4-dihydropyridazin-4-yl, 1,4-dihydropyridazin-5-yl, 1,4-dihydropyridazin-6-yl, 1,4-dihydropyrazin-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-4-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;

N-bound, 5-membered, partially unsaturated rings, such as 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-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-tetrahydropyrimidin-3-yl, 1,2,3,4-tetrahydropyrazin-1-yl, 1,2,3,4-tetrahydropyrimidin-1-yl, 1,2,3,4-tetrahydropyrimidin-3-yl, 2,3-dihdro-1,4-thiazin-4-yl, 2H-1,2-oxazin-2-yl, 2H-1,2-thiazin-2-yl, 4H-1,4-oxazin-4-yl, 4H-1,4-thiazin-4-yl, 1,4-dihydropyridazin-1-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, imidazol-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-oxadiazol-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;

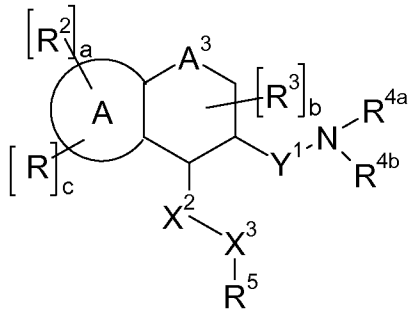
N-bound, 5-membered, heteroaromatic rings, such as
pyrrol-1-yl, pyrazol-1-yl, imidazol-1-yl, 1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, tetrazol-1-yl.

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 carbocycle, such as a benzene, cyclohexane, cyclohexene or cyclohexadiene ring, or a futher anellated 5- or 6-membered heterocyclic ring, this heterocyclic ring being saturated or unsaturated or aromatic. These include quinolinyl, isoquinolinyl, indolyl, indolizinyl, isoindolyl, indazolyl, benzofuryl, benzthienyl, benzo[b]thiazolyl, benzoxazolyl, benzthiazolyl and benzimidazolyl. Examples of 5- or 6-membered heteroaromatic compounds comprising an anellated cycloalkenyl ring include dihydroindolyl, dihydroindolizinyl, dihydroisoindolyl, dihydroquinolinyl, dihydroisoquinolinyl, chromenyl and chromanyl.

C_3-C_{12}-Heteroarylene is a heteroaryl diradical. Examples include pyrid-2,5-ylene and pyrid-2,4-ylene.

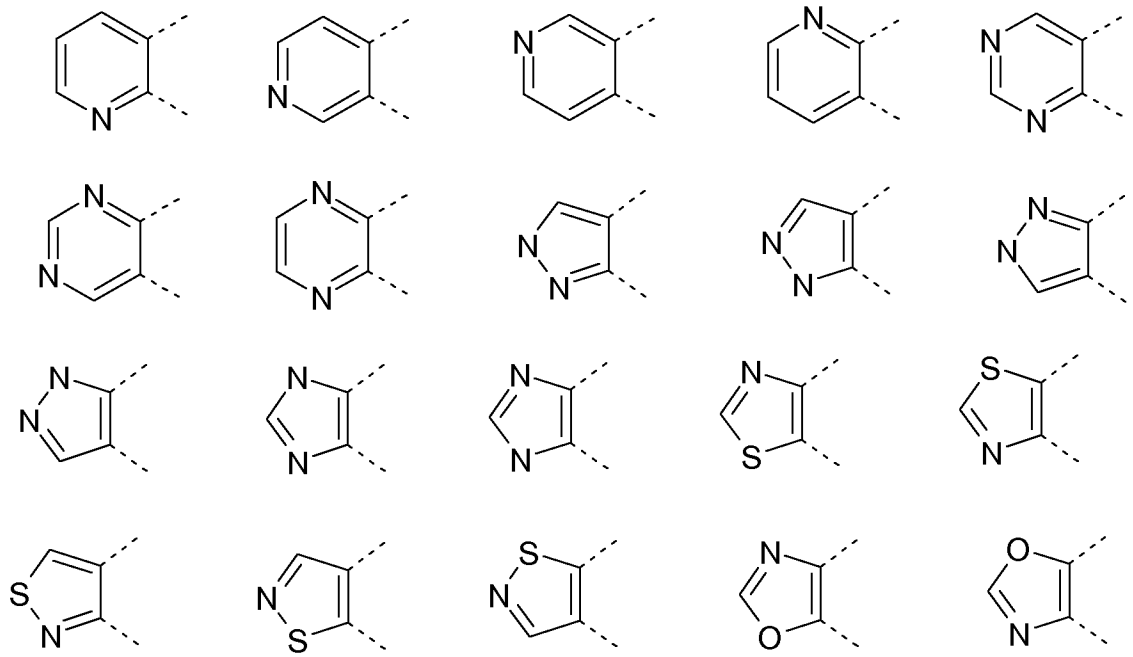
With respect to the compounds' capability of inhibiting glycine transporter 1, the variables A, R, R^1, W, A^1, Q, Y, A^2, X^1, R^2, A^3, R^3, Y^1, R^{4a}, R^{4b}, X^2, X^3, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18} preferably have the following meanings which, when taken alone or in combination, represent particular embodiments of the compounds of the formula (I), (II), (III) or any other formula disclosed herein.

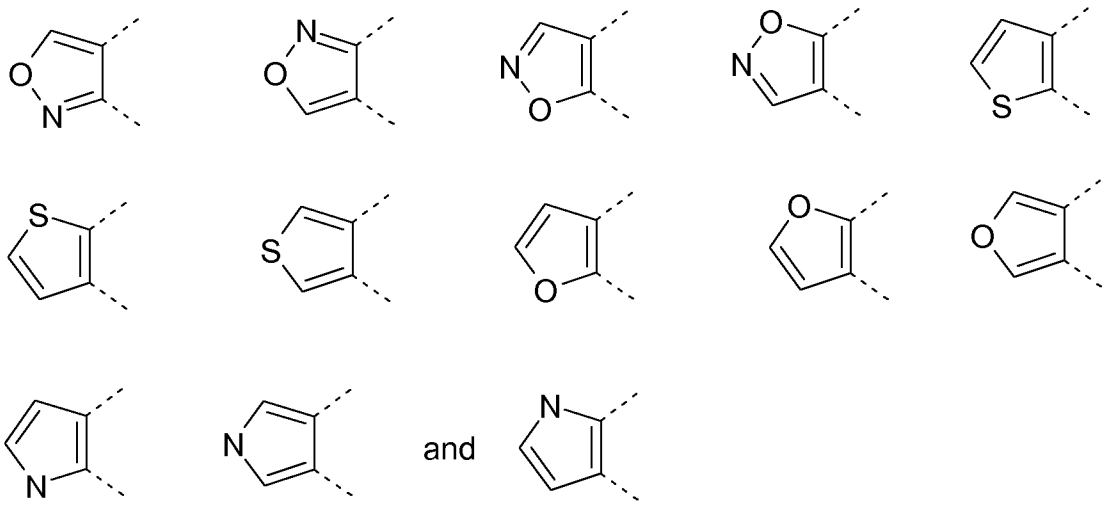
In said formula (I), (II) or (III), there may be one or more than one substituent R, R^2 and/or R^3. More particularly, there may be up to 3 substituents R^2, and up to 4 substituents R^3. Preferably there is one substituent R and 1, 2 or 3 substituents R^2. Formula (I) may thus be depicted as follows:



wherein a is 1, 2 or 3, b is 1, 2, 3 or 4 and c is 1. 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.

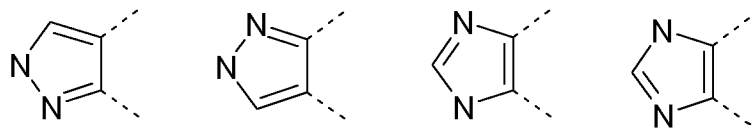
A is a 5- or 6-membered ring which includes two carbon atoms from the cyclopentane, cyclohexane or cycloheptane moiety to which A is fused. A may be a homocyclic or heterocyclic ring. The ring may be saturated, unsaturated non-aromatic or aromatic. According to a particular embodiment, A is a benzene 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:



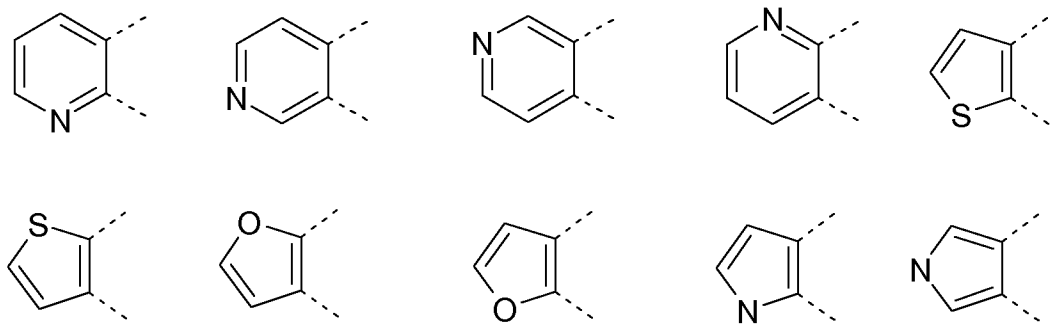


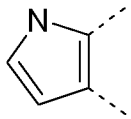
In said formulae, hydrogen atoms are not depicted. This is meant to illustrate that the free valency of a carbon or nitrogen atom may be either bound to a hydrogen atom, to R or to R^2. Accordingly, R and R^2 may be C- or N-bound at any position of ring A.

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:

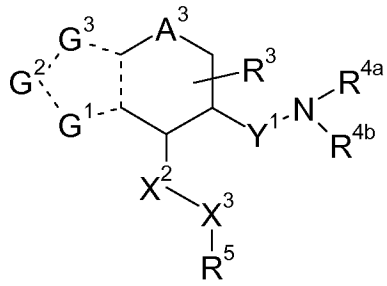


Preferably, A is a heterocyclic ring selected from the group consisting of the following 5- or 6-membered heterocyclic rings:



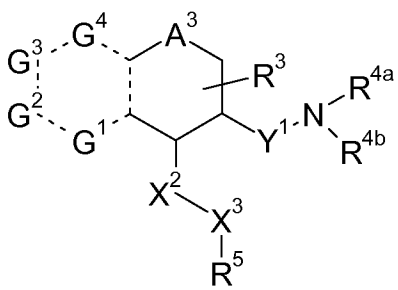
and 

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:



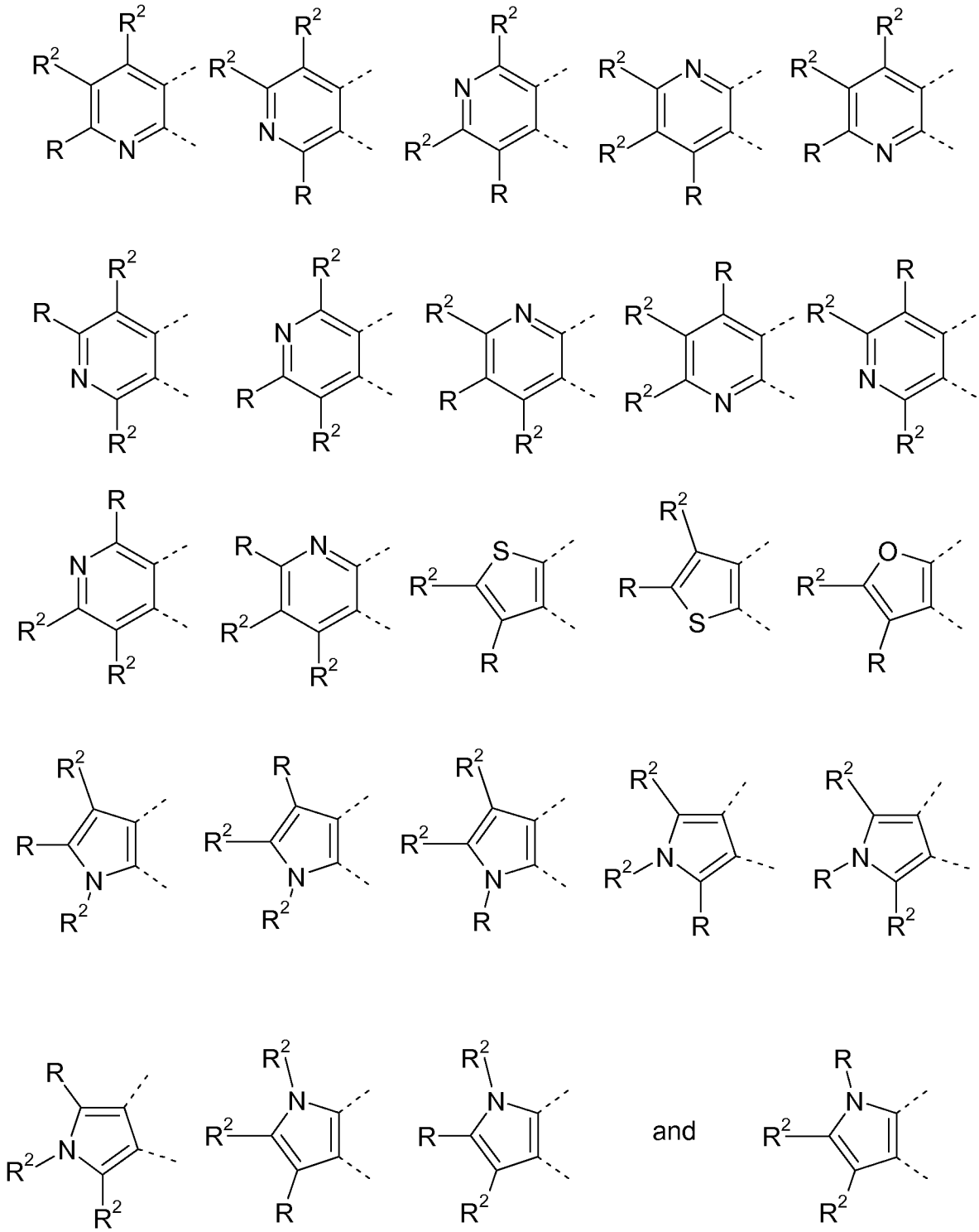
In said formula, G^1, G^2 and G^3 independently are –CH=, $-CH_2-$, -N=, -NH-, S or O, at least one of G^1, G^2 and G^3 is –CH= or $-CH_2-$, the dotted line represents a single or a double bond and A^3, R^3, Y^1, R^{4a}, R^{4b}, X^2, X^3, R^5 are as defined herein.

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:

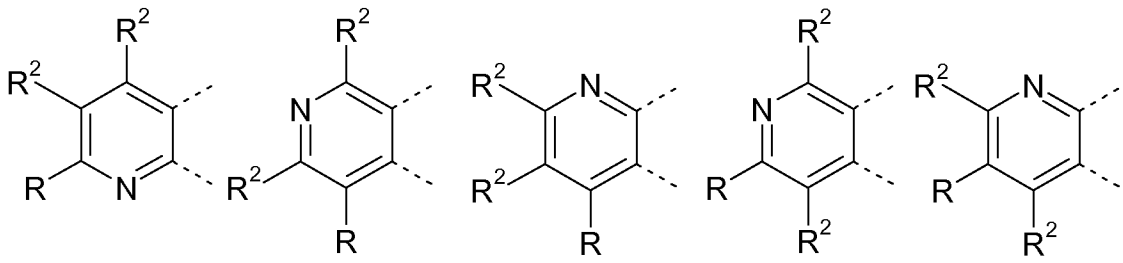


In said formula, G^1, G^2, G^3 and G^4 independently are –CH=, -CH_2-, -N=, -NH-, S or O, at least one of G^1, G^2, G^3 and G^4 is –CH= or -CH_2-, the dotted line represents a single or a double bond and A^3, R^3, Y^1, R^{4a}, R^{4b}, X^2, X^3, R^5 are as defined herein.

Heterocyclic compounds having the following partial structures are preferred:



Heterocyclic compounds having the following partial structures are particularly preferred:



In said formulae, R and R^2 are as defined herein. If there is more than one radical R^2, these may be the same or different radicals.

R is R^1-W-A^1-Q-Y-A^2-X^1- and A, R^1, W, A^1, Q, Y, A^2, X^1, R^2, A^3, R^3, Y^1, R^{4a}, R^{4b}, X^2, X^3, R^5 are as defined herein.

R^1 is hydrogen, C_1-C_6-alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl or n-pentyl), C_3-C_{12}-cycloalkyl-C_1-C_4-alkyl (e.g. cyclopropylmethyl, cyclopentylmethyl or cyclohexylmethyl), halogenated C_1-C_6-alkyl (e.g. 3-fluoroprop-1-yl, 3-chloroprop-1-yl or 3,3,3-trifluoroprop-1-yl), tri-(C_1-C_4-alkyl)-silyl-C_1-C_4-alkyl (e.g. trimethylsilylethyl), hydroxy-C_1-C_4-alkyl, C_1-C_6-alkoxy-C_1-C_4-alkyl (e.g. ethoxyethyl), amino-C_1-C_4-alkyl, C_1-C_6-alkylamino-C_1-C_4-alkyl, di-C_1-C_6-alkylamino-C_1-C_4-alkyl, C_1-C_6-alkylcarbonylamino-C_1-C_4-alkyl, C_1-C_6-alkyloxycarbonylamino-C_1-C_4-alkyl, C_1-C_6-alkylaminocarbonylamino-C_1-C_4-alkyl, di-C_1-C_6-alkylaminocarbonylamino-C_1-C_4-alkyl, C_1-C_6-alkylsulfonylamino-C_1-C_4-alkyl, (optionally substituted C_6-C_{12}-aryl-C_1-C_6-alkyl)amino-C_1-C_4-alkyl, optionally substituted C_6-C_{12}-aryl-C_1-C_4-alkyl, optionally substituted C_3-C_{12}-heterocyclyl-C_1-C_4-alkyl, C_3-C_{12}-cycloalkyl (e.g. cyclopropyl or cyclobutyl), C_1-C_6-alkylcarbonyl, C_1-C_6-alkoxycarbonyl, halogenated C_1-C_6-alkoxycarbonyl, C_6-C_{12}-aryloxycarbonyl, aminocarbonyl, C_1-C_6-alkylaminocarbonyl, (halogenated C_1-C_4-alkyl)aminocarbonyl, C_6-C_{12}-arylaminocarbonyl, C_2-C_6-alkenyl (e.g. prop-1,2-en-1-yl), C_2-C_6-alkynyl, optionally substituted C_6-C_{12}-aryl (e.g. phenyl, 2-methylphenyl), hydroxy, C_1-C_6-alkoxy (e.g. tert-butyloxy), halogenated C_1-C_6-alkoxy, C_1-C_6-hydroxyalkoxy, C_1-C_6-alkoxy-C_1-C_4-alkoxy, amino-C_1-C_4-alkoxy, C_1-C_6-alkylamino-C_1-C_4-alkoxy, di-C_1-C_6-alkylamino-C_1-C_4-alkoxy, C_1-C_6-alkylcarbonylamino-C_1-C_4-alkoxy, C_6-C_{12}-arylcarbonylamino-C_1-C_4-alkoxy, C_1-C_6-alkoxycarbonylamino-C_1-C_4-alkoxy, C_6-C_{12}-aryl-C_1-C_4-alkoxy, C_1-C_6-alkylsulfonylamino-C_1-C_4-alkoxy, (halogenated C_1-C_6-alkyl)sulfonylamino-C_1-C_4-alkoxy, C_6-C_{12}-arylsulfonylamino-C_1-C_4-alkoxy, (C_6-C_{12}-aryl-C_1-C_6-alkyl)sulfonylamino-C_1-C_4-alkoxy, C_3-C_{12}-heterocyclylsulfonylamino-C_1-C_4-alkoxy, C_3-C_{12}-heterocyclyl-C_1-C_4-alkoxy, C_6-C_{12}-aryloxy, C_3-C_{12}-heterocyclyloxy, C_1-C_6-alkylthio, halogenated C_1-C_6-alkylthio, C_1-C_6-alkylamino, (halogenated C_1-C_6-alkyl)amino, di-C_1-C_6-alkylamino (e.g. dimethylamino), di-(halogenated C_1-C_6-alkyl)amino, C_1-C_6-alkylcarbonylamino, (halogenated C_1-C_6-alkyl)carbonylamino, C_6-C_{12}-arylcarbonylamino, C_1-C_6-alkylsulfonylamino, (halogenated C_1-C_6-alkyl)sulfonylamino, C_6-C_{12}-arylsulfonylamino or optionally substituted C_3-C_{12}-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 or 1-methyl-1,2,4-triazol-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).

Preferably, R^1 is C_1-C_6-alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, sec-butyl, n-butyl or n-pentyl), C_3-C_{12}-cycloalkyl-C_1-C_4-alkyl (e.g. cyclopropylmethyl, cyclopentylmethyl or cyclohexylmethyl), halogenated C_1-C_6-alkyl (e.g. 3-fluoroprop-1-yl, 3-chloroprop-1-yl or 3,3,3-trifluoroprop-1-yl), tri-(C_1-C_4-alkyl)-silyl-C_1-C_4-alkyl (e.g. trimethylsilylethyl), C_1-C_6-alkoxy-C_1-C_4-alkyl (e.g. ethoxyethyl), amino-C_1-C_4-alkyl, C_1-C_6-alkylamino-C_1-C_4-alkyl, di-C_1-C_6-alkylamino-C_1-C_4-alkyl, C_1-C_6-alkyloxycarbonylamino-C_1-C_4-alkyl, C_1-C_6-alkylaminocarbonylamino-C_1-C_4-alkyl, C_6-C_{12}-aryl-C_1-C_4-alkyl, C_3-C_{12}-cycloalkyl (e.g. cyclopropyl or cyclobutyl), C_2-C_6-alkenyl (e.g. prop-1,2-en-1-yl), optionally substituted C_6-C_{12}-aryl (e.g. phenyl), hydroxy, C_1-C_6-alkylamino, (halogenated C_1-C_6-alkyl)amino, di-C_1-C_6-alkylamino or optionally substituted C_3-C_{12}-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 or 3-pyrrolidinyl, 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).

In particular, R^1 is C_1-C_6-alkyl (e.g. n-propyl, isopropyl, 2-butyl), C_3-C_{12}-cycloalkyl-C_1-C_4-alkyl (e.g. cyclopropylmethyl), C_3-C_{12}-cycloalkyl (e.g. cyclobutyl), or optionally substituted C_3-C_{12}-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, 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).

In connection with R^1, substituted C_6-C_{12}-aryl in particular includes C_6-C_{12}-aryl, such as phenyl or naphthyl, substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, amino, C_1-C_4-alkylamino, C_1-C_4-dialkylamino, morpholino and piperidinyl. The same applies to substituted C_6-C_{12}-aryl in substituted C_6-C_{12}-aryl-C_1-C_4-alkyl.

In connection with R^1, substituted C_3-C_{12}-heterocyclyl in particular includes C_3-C_{12}-heterocyclyl, such as pyridyl, thienyl, diazolyl, quinolinyl, furanyl, thiophenyl, piperidinyl, piperazinyl or morpholinyl, pyrrolyl, isoxazolyl and triazolyl being further examples of such C_3-C_{12}-heterocyclyl, substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxycarbonyl, cyano, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkylsulfonyl, amino, C_1-C_4-alkylamino, C_1-C_4-dialkylamino, C_6-C_{12}-arylamino and C_3-C_{12}-heterocyclyl (e.g., morpholino or piperidinyl). The same applies to substituted C_3-C_{12}-heteroaryl in substituted C_3-C_{12}-heteroaryl-C_1-C_4-alkyl.

According to one embodiment, W is $-NR^8-$ and Y is a bond. According to an alternative embodiment, W is a bond and Y is $-NR^9-$. According to a further alternative embodiment, W is a bond and Y is a bond, especially if R^1 is a nitrogen-bound radical, e.g. nitrogen-bound heterocyclyl such as piperazinyl or morpholinyl.

According to one embodiment, Q is $-S(O)_2-$. According to an alternative embodiment, Q is $-C(O)-$.

According to a particular embodiment, $-W-A^1-Q-Y-$ is $-W-A^1-S(O)_2-NR^9-$, $-NR^8-S(O)_2-$, $-A^1-S(O)_2-$ or $-S(O)_2-$. According to a further particular embodiment, $-W-A^1-Q-Y-$ is $-W-A^1-CO-NR^9-$ or $-NR^8-CO-$.

A^1 is optionally substituted C_1-C_4-alkylene or a bond. In connection with A^1, substituted C_1-C_4-alkylene in particular includes C_1-C_4-alkylene substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, C_1-C_4-alkyl and cyano. Preferably, A^1 is a bond. If A^1 is C_1-C_4-alkylene, W is preferably $-NR^8-$.

A^2 is optionally substituted C_1-C_4-alkylene (e.g. 1,2-ethylene or 1,3-propylene), C_1-C_4-alkylene-CO-, -CO-C_1-C_4-alkylene, C_1-C_4-alkylene-O-C_1-C_4-alkylene, C_1-C_4-alkylene-NR^{10}-C_1-C_4-alkylene, optionally substituted C_6-C_{12}-arylene, optionally substituted C_6-C_{12}-heteroarylene or a bond. Additionally, A^2 may be optionally substituted C_2-C_4-alkenylene or optionally substituted C_2-C_4-alkynylene. Preferably, A^2 is optionally substituted C_1-C_4-alkylene (e.g. 1,2-ethylene or 1,3-propylene). More preferably, A^2 is C_1-C_4-alkylene (e.g. 1,2-ethylene). Alternatively, it is preferred that A^2 is optionally substituted C_6-C_{12}-arylene, in particular C_6-C_{12}-arylene selected from the group consisting of phen-1,4-ylene and phen-1,3-ylene, or optionally substituted C_6-C_{12}-heteroarylene, in particular C_6-C_{12}-heteroarylene selected from the group consisting of pyrid-2,5-ylene and pyrid-2,4-ylene. If A^2 is a bond, X^1 is preferably optionally substituted C_1-C_4-alkylene. Alternatively, if A^2 is a bond, X^1 is in particular optionally substituted C_2-C_4-alkenylene or optionally substituted C_2-C_4-alkynylene.

In connection with A^2, substituted C_1-C_4-alkylene in particular includes C_1-C_4-alkylene substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl and cyano.

In connection with A^2, substituted C_2-C_4-alkenylene or substituted C_2-C_4-alkynylene in particular includes C_2-C_4-alkenylene or C_2-C_4-alkynylene substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl and cyano.

In connection with A^2, substituted C_6-C_{12}-arylene in particular includes C_6-C_{12}-arylene substituted with 1, 2 or 3 substituents selected from the group consisting of C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxycarbonyl, cyano, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkylsulfonyl, amino, C_1-C_4-alkylamino, C_1-C_4-dialkylamino, C_6-C_{12}-arylamino and C_3-C_{12}-heterocyclyl (e.g., morpholino or piperidinyl).

In connection with A^2, substituted C_6-C_{12}-heteroarylene in particular includes C_6-C_{12}-heteroarylene substituted with 1, 2 or 3 substituents selected from the group consisting of C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxycarbonyl, cyano, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkylsulfonyl, amino, C_1-C_4-alkylamino, C_1-C_4-dialkylamino, C_6-C_{12}-arylamino and C_3-C_{12}-heterocyclyl (e.g, morpholino or piperidinyl).

X^1 is -O-, -NR^{11}-, -S- or optionally substituted C_1-C_4-alkylene (e.g. -CH_2-, 1,2-ethylene and 1,3-propylene). In connection with X^1, substituted C_1-C_4-alkylene in particular includes C_1-C_4-alkylene substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl and cyano. Additionally, X^1 may be optionally substituted C_2-C_4-alkenylen or optionally substituted C_2-C_4-alkynylene (e.g. propynylene). In connection with X^1, substituted C_2-C_4-alkenylene or substituted C_2-C_4-alkynylene in particular includes C_2-C_4-alkenylene or C_2-C_4-alkynylene substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl and cyano. Preferably, X^1 is -O-, -NR^{11}, -S-. More preferably, X^1 is -O-. Alternatively, it is preferred if X^1 is optionally substituted C_1-C_4-alkylene (e.g. -CH_2- or 1,2-ethylene).

According to a particular embodiment, A^2 is a bond and X^1 is optionally substituted C_1-C_4-alkylene, optionally substituted C_2-C_4-alkenylene or optionally substituted C_2-C_4-alkynylene.

According to a particular embodiment, R^1-W-A^1-Q-Y-A^2-X^1- is R^1-$S(O)_2$-NH-A^2-X^1-, R^1-NH-$S(O)_2$-A^2-X^1-, R^1-C(O)-NH-A^2-X^1- or R^1-NH-C(O)-A^2-X^1-.

According to a particular embodiment, the structural element -Y-A^2-X^1- comprises at least 2, 3 or 4 atoms in the main chain. According to further particular embodiments the struc-

tural element -Y-A^2-X^1- has up to 4, 5 or 6 atoms in the main chain, such as 2 to 6, 2 to 5 or 2 to 4 atoms in the main chain, especially 2, 3 or 4 atoms in the main chain.

According to a further particular embodiment, -Y-A^2-X^1- is -C_1-C_4-alkylene-O- or -NR^9-C_1-C_4-alkylene-O-, with -Y-A^2-X^1- preferably having 2 to 6, 3 to 5 and especially 4 atoms in the main chain. Particular examples of -Y-A^2-X^1- include -$(CH_2)_3$-O- and -NR^9-$(CH_2)_2$-O-. In this particular embodiment, R^9 is as defined herein and preferably R^9 is hydrogen, C_1-C_6-alkyl (e.g. methyl or ethyl) or C_3-C_{12}-cycloalkyl (e.g. cyclopropyl), or R^9 is C_1-C_4-alkylene that is bound to a carbon atom in A^2 which is C_1-C_4-alkylene.

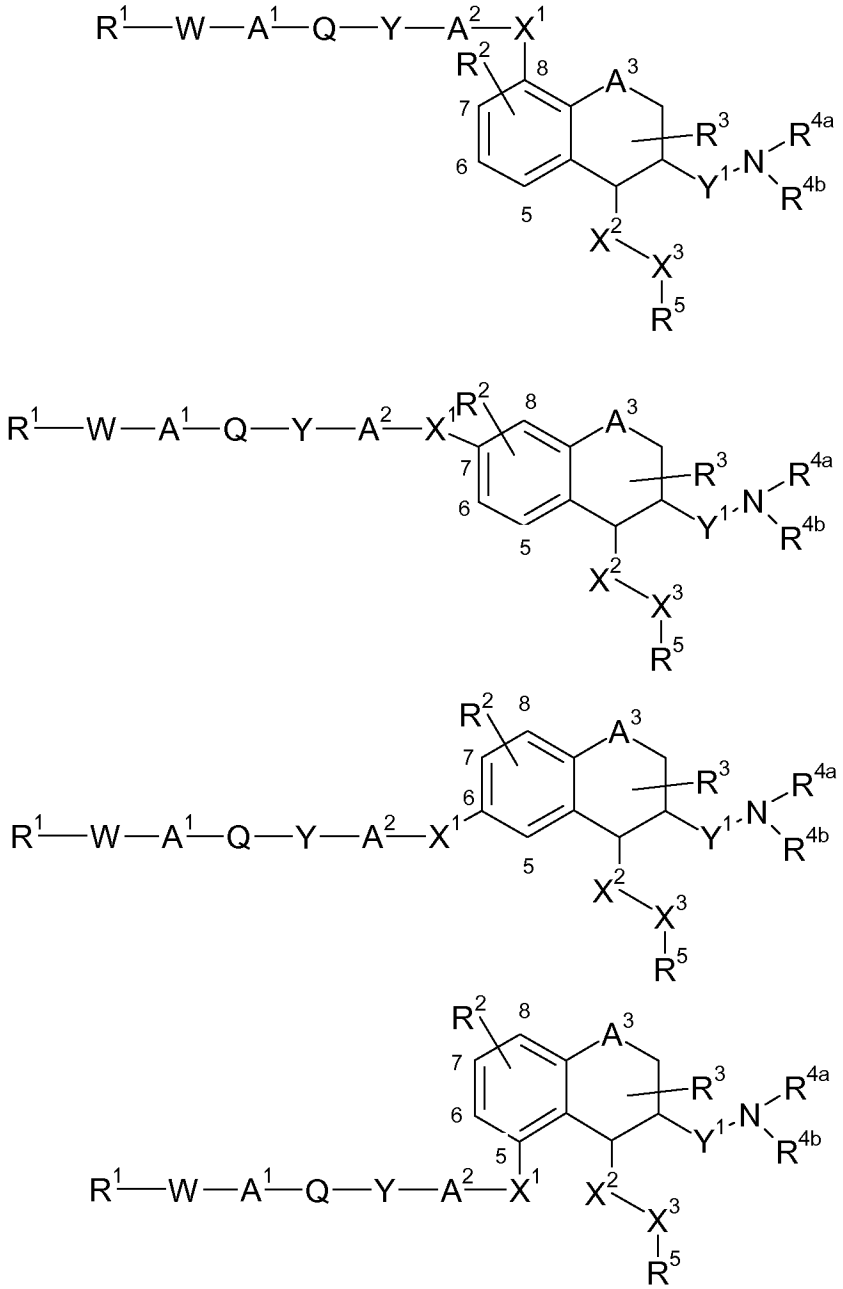
According to a further particular embodiment, -Y-A^2-X^1- is -NR^9-C_1-C_4-alkylene- (e.g. -NH-CH_2-, -NH-$(CH_2)_2$- or -NH-$(CH_2)_3$-), with -Y-A^2-X^1- preferably having 2 to 6, 2 to 5, 2 to 4 and especially 2, 3 or 4 atoms in the main chain. In this particular embodiment, R^9 is as defined herein and preferably R^9 is hydrogen, C_1-C_6-alkyl (e.g. methyl or ethyl) or C_3-C_{12}-cycloalkyl (e.g. cyclopropyl); or R^9 is C_1-C_4-alkylene that is bound to a carbon atom in X^1 which is C_1-C_4-alkylene.

According to a further particular embodiment, -Y-A^2-X^1- is -NR^9-C_2-C_4-alkenylene- or -NR^9-C_2-C_4-alkynylene- (e.g. -NH-CH_2-C≡C-), with -Y-A^2-X^1- preferably having 2 to 6, 3 to 5 and especially 4 atoms in the main chain. In this particular embodiment, R^9 is as defined herein and preferably is R^9 is hydrogen, C_1-C_6-alkyl (e.g. methyl or ethyl) or C_3-C_{12}-cycloalkyl (e.g. cyclopropyl or cyclobutyl). If A is a heterocyclic ring, this embodiment of -Y-A^2-X^1- is particularly suitable.

According to a further particular embodiment, -Y-A^2-X^1- is -C_1-C_4-alkylene- (e.g. -$(CH_2)_2$-), with -Y-A^2-X^1- preferably having 2 to 6, 2 to 5, 2 to 4 and especially 2 atoms in the main chain. If A is a heterocyclic ring, this embodiment of -Y-A^2-X^1- is particularly suitable.

According to a further particular embodiment, the structural motif -Y-A^2-X^1 as disclosed herein is bound to Q being -$S(O)_2$- or -C(O)-. Particular examples for this embodiment include heterocyclic compounds of the invention wherein R is R^1-$S(O)_2$-Y-A^2-X^1 or R^1-C(O)-Y-A^2-X^1.

The radical R and in particular the radical R^1-W-A^1-Q-Y-A^2-X^1- may, in principle, be bound to the 5-, 6-, 7- or 8-position of the skeleton of the compounds of the invention:

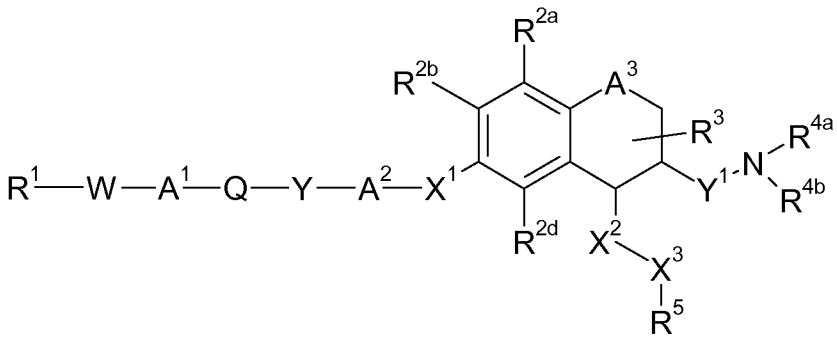


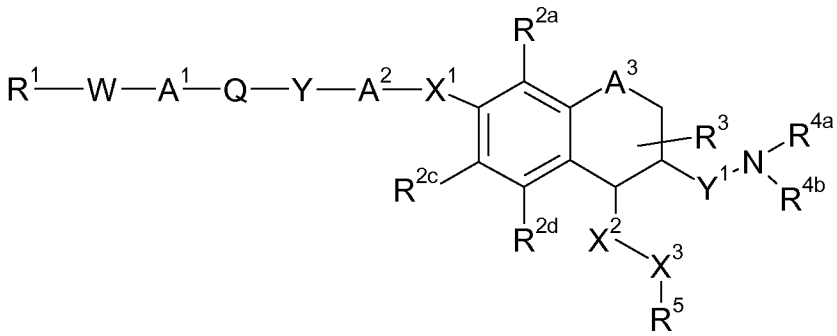
In said formulae, R^1, W, A^1, Q, Y, A^2, X^1, R^2, A^3, R^3, Y^1, R^{4a}, R^{4b}, X^2, X^3, R^5 are as defined herein.

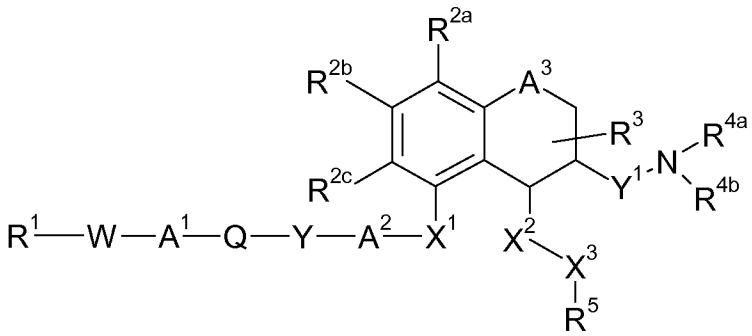
Compounds of the invention having the radical R^1-W-A^1-Q-Y-A^2-X^1- in the 5-, 6-, 7-position are preferred.

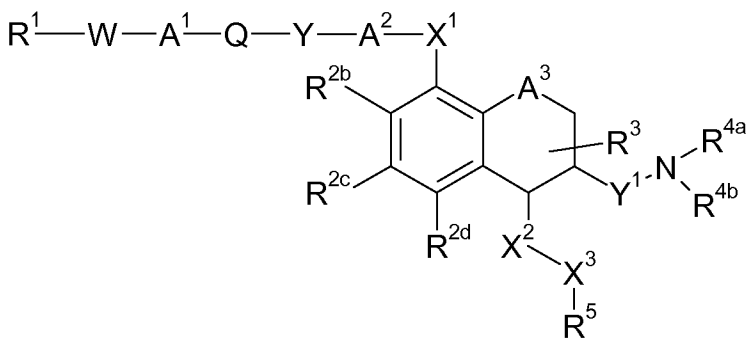
Particularly preferred are compounds of the invention having the radical R^1-W-A^1-Q-Y-A^2-X^1- in the 6-position.

In addition to the radical R^1-W-A^1-Q-Y-A^2-X^1-, 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, in 5-, 6-, 7- and/or 8-position, the skeleton of the compounds of the invention may be substituted with one or more than one radical R^2. The compounds of the invention may therefore be represented by one of the following formulae:









wherein R^{2a}, R^{2b}, R^{2c}, R^{2d} independently have one of the meanings given for R^2, and R^1, W, A^1, Q, Y, A^2, X^1, R^2, A^3, R^3, Y^1, R^{4a}, R^{4b}, X^2, X^3, R^5 are as defined herein.

R^2 is hydrogen, halogen (e.g. fluorine), C_1-C_6-alkyl, halogenated C_1-C_4-alkyl, hydroxy-C_1-C_4-alkyl, -CN, C_2-C_6-alkenyl, C_2-C_6-alkynyl, optionally substituted C_6-C_{12}-aryl, hydroxy, C_1-C_6-alkoxy, halogenated C_1-C_6-alkoxy, C_1-C_6-alkoxycarbonyl, C_2-C_6-alkenyloxy, C_6-C_{12}-aryl-C_1-C_4-alkoxy, C_1-C_6-alkylcarbonyloxy, C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl, aminosulfonyl, amino, C_1-C_6-alkylamino, C_2-C_6-alkenylamino, nitro or optionally substituted C_3-C_{12}-heterocyclyl, or two radicals R^2 together with the ring atoms to which they are bound form a 5- or 6 membered ring.

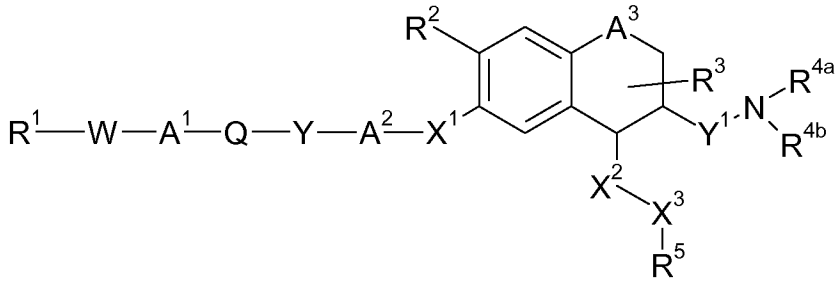
An optionally substituted 5- or 6-membered ring that is formed by two radicals R^2 together with the ring atoms of A to which they are bound is, for instance, a benzene ring.

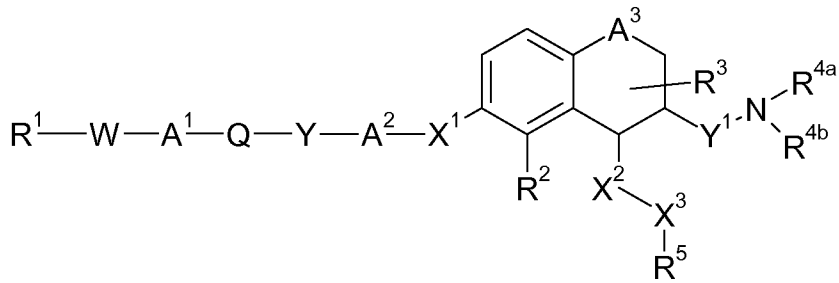
In connection with R^2, substituted C_6-C_{12}-aryl in particular includes C_6-C_{12}-aryl, such as phenyl, substituted with 1, 2 or 3 substituents selected from the group consisting of halogen and C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, C_1-C_4-alkoxy and C_1-C_4-haloalkoxy.

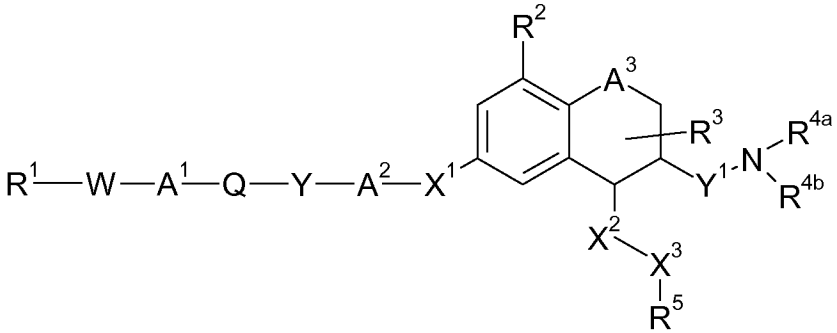
In connection with R^2, substituted C_3-C_{12}-heterocyclyl in particular includes C_3-C_{12}-heterocyclyl, such as morpholinyl, pyrrolidinyl and piperidinyl, substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, C_1-C_4-alkoxy and C_1-C_4-haloalkoxy.

Preferably, R^2 is hydrogen, halogen (e.g. fluorine) or C_1-C_6-alkoxy. In particular, R^2 is hydrogen or halogen (e.g. fluorine).

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



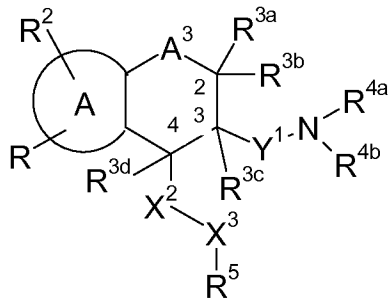




wherein R^1, W, A^1, Q, Y, A^2, X^1, R^2, A^3, R^3, Y^1, R^{4a}, R^{4b}, X^2, X^3, R^5 are as defined herein.

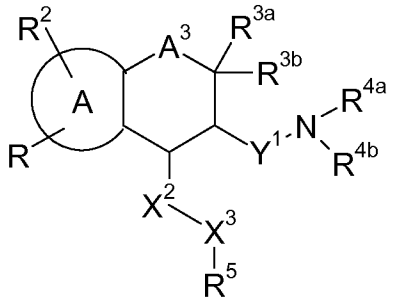
A^3 is -O-, -S- or -NR^{16}-. According to a preferred embodiment, A^3 is -O-.

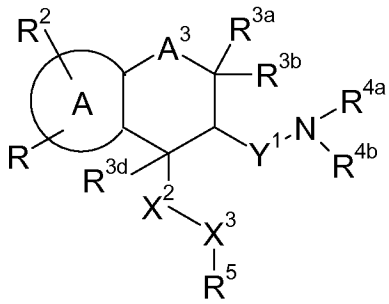
In 2-, 3- and/or 4-position, the compounds of the invention may be substituted with one or more than one radical R^3. If there is more than one radical R^3, these may be the same or different radicals. The compounds of the invention may therefore be represented by the following formula:

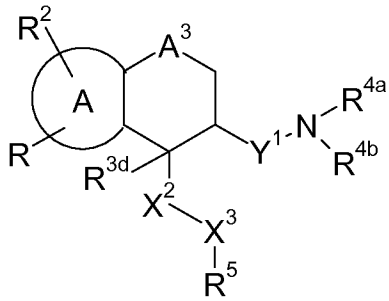


wherein R^{3a}, R^{3b}, R^{3c}, R^{3d} independently have one of the meanings given for R^3, and A, R, R^2, A^3, R^3, Y^1, R^{4a}, R^{4b}, X^2, X^3, R^5 are as defined herein.

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







wherein R^{3a}, R^{3b}, R^{3d} independently have the meaning of R^3 and A, R, R^2, A^3, R^3, Y^1, R^{4a}, R^{4b}, X^2, X^3, R^5 are as defined herein.

R^3 is hydrogen, halogen, C_1-C_6-alkyl, C_1-C_6-alkoxy, or two radicals R^3 together with the carbon atom to which they are attached form a carbonyl group.

Preferably, R^3 is hydrogen or C_1-C_6-alkyl (e.g. methyl). In particular, R^3 is hydrogen.

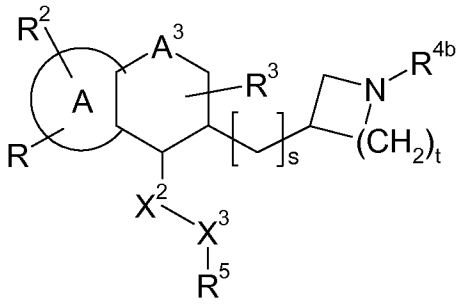
Y^1 is a bond or optionally substituted C_1-C_4-alkylene (e.g. methylene or 1,2-ethylene). In connection with Y^1, substituted C_1-C_4-alkylene in particular includes C_1-C_4-alkylene substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_3-C_{12}-cycloalkyl and cyano. In particular, Y^1 is a bond.

R^{4a} is hydrogen, C_1-C_6-alkyl (e.g. methyl, ethyl, n-propyl or isopropyl), C_3-C_{12}-cycloalkyl-C_1-C_4-alkyl (e.g. cyclopropylmethyl), halogenated C_1-C_4-alkyl (e.g. 2-fluoroethyl or 2,2,2-trifluoroethyl), hydroxy-C_1-C_4-alkyl, C_1-C_6-alkoxy-C_1-C_4-alkyl, amino-C_1-C_4-alkyl, CH_2CN, C_6-C_{12}-aryl-C_1-C_4-alkyl (e.g. benzyl), C_3-C_{12}-cycloalkyl (e.g. cyclopropyl), -CHO, C_1-C_4-alkylcarbonyl (e.g. methylcarbonyl, ethylcarbonyl or isopropylcarbonyl), (halogenated C_1-C_4-alkyl)carbonyl (e.g. fluoromethylcarbonyl, difluoromethylcarbonyl, trifluoromethylcarbonyl, 1,1,1-trifluoroeth-2-ylcarbonyl or 1,1,1-trifluoroprop-3-ylcarbonyl), C_6-C_{12}-arylcarbonyl (e.g. phenylcarbonyl), C_1-C_4-alkoxycarbonyl (e.g. ethoxycarbonyl or tert-butyloxycarbonyl), C_6-C_{12}-aryloxycarbonyl (e.g. phenoxycarbonyl), C_1-C_6-alkylaminocarbonyl, C_2-C_6-alkenyl, -C(=NH)NH_2, -C(=NH)NHCN, C_1-C_6-alkylsulfonyl, C_6-C_{12}-arylsulfonyl, amino, -NO or C_3-C_{12}-heterocyclyl (e.g. 3-oxetanyl).

Preferably, R^{4a} is hydrogen, C_1-C_6-alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, 2-methyl-but-4-yl, or 2-methyl-prop-3-yl), C_3-C_{12}-cycloalkyl-C_1-C_4-alkyl (e.g. cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, 1-cyclopropyl-eth-2-yl, 1-cyclopentyl-eth-2-yl, or cyclohexylmethyl), halogenated C_1-C_4-alkyl (e.g. 2-fluoroethyl or 2,2,2-trifluoroethyl), amino-C_1-C_4-alkyl, CH_2CN,C_6-C_{12}-aryl-C_1-C_4-alkyl (e.g. benzyl), C_3-C_{12}-cycloalkyl (e.g. cyclopropyl), C_1-C_4-alkylcarbonyl (e.g. methylcarbonyl or isopropylcarbonyl), (halogenated C_1-C_4-alkyl)carbonyl (e.g. fluoromethylcarbonyl, difluoromethylcarbonyl or trifluoromethylcarbonyl), C_6-C_{12}-arylcarbonyl (e.g. phenylcarbonyl), C_1-C_4-alkoxycarbonyl (e.g. ethoxycarbonyl or tert-butyloxycarbonyl), C_6-C_{12}-aryloxycarbonyl (e.g. phenoxycarbonyl), -C(=NH)NH_2, -C(=NH)NHCN, C_1-C_6-alkylsulfonyl, amino, -NO or C_3-C_{12}-heterocyclyl (e.g. 3-oxetanyl).

In particular, R^{4a} is hydrogen, C_1-C_6-alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, 2-methyl-but-4-yl, or 2-methyl-prop-3-yl), C_3-C_{12}-cycloalkyl (e.g. cyclopropyl), C_3-C_{12}-cycloalkyl-C_1-C_4-alkyl (e.g. cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, 1-cyclopropyl-eth-2-yl, 1-cyclopentyl-eth-2-yl, or cyclohexylmethyl), or C_3-C_{12}-heterocyclyl (e.g. 3-oxetanyl).

Alternatively, R^{4a} is optionally substituted C_1-C_4-alkylene (e.g. methylene or 1,2-ethylene) that is bound to a carbon atom in Y^1. In connection with R^{4a}, substituted C_1-C_4-alkylene in particular includes C_1-C_4-alkylene substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, hydroxy and C_1-C_4-alkoxy. In particular, R^{4a} is C_1-C_4-alkylene (e.g. methylene or 1,2-ethylene) that is bound to a carbon atom in Y^1 with Y^1 being optionally substituted C_1-C_4-alkylene (e.g. 1,2-ethylene or 1,3-propylene) so that R^{4a} and at least part of Y^1 together with the nitrogen atom to which R^{4a} and Y^1 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, R, R^2, A^3, R^3, R^{4b}, X^2, X^3, R^5 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.

R^{4b} is hydrogen, C_1-C_6-alkyl (e.g. methyl, ethyl), halogenated C_1-C_4-alkyl, hydroxy-C_1-C_4-alkyl, C_1-C_6-alkoxy-C_1-C_4-alkyl, amino-C_1-C_4-alkyl, CH_2CN, -CHO, C_1-C_4-alkylcarbonyl, (halogenated C_1-C_4-alkyl)carbonyl, C_6-C_{12}-arylcarbonyl, C_1-C_4-alkoxycarbonyl, C_6-C_{12}-aryloxycarbonyl, C_1-C_6-alkylaminocarbonyl, C_2-C_6-alkenyl, -C(=NH)NH_2, -C(=NH)NHCN, C_1-C_6-alkylsulfonyl, C_6-C_{12}-arylsulfonyl, amino, -NO or C_3-C_{12}-heterocyclyl.

Preferably, R^{4b} is hydrogen or C_1-C_6-alkyl (e.g. methyl). In particular, R^{4b} is hydrogen.

Alternatively, R^{4a}, R^{4b} together are optionally substituted C_1-C_6-alkylene (e.g. 1,4-butylene, 1,3-propylene, 2-fluoro-but-1,4-ylene, 1-oxo-but-1,4-ylene, 2-methyl-1,3-propylene, 2,2-dimethyl-1,3-propylene, or 2-methyl-2-hydroxy-1,3-propylene), wherein one -CH_2- of C_1-C_6-alkylene may be replaced by an oxygen atom (e.g. -CH_2-CH_2-O-CH_2-CH_2-) or -NR^{17}.

In connection with R^{4a} and R^{4b}, substituted C_1-C_6-alkylene in particular includes C_1-C_6-alkylene substituted with 1, 2 or 3 substituents selected from the group consisting of halogen (e.g. fluoro or chloro), C_1-C_4-alkyl (e.g. methyl), cyano, hydroxy and C_1-C_4-alkoxy.

X^2 is -O-, -NR^6-, -S-, >$CR^{12a}R^{12b}$ or a bond. Preferably, X^2 is >$CR^{12a}R^{12b}$.

X^3 is -O-, -NR^7-, -S-, >$CR^{13a}R^{13b}$ or a bond. Preferably, X^3 is a bond.

Thus, it is preferred if X^2 is >$CR^{12a}R^{12b}$ and X^3 is a bond.

R^{12a} is hydrogen, optionally substituted C_1-C_6-alkyl, C_1-C_6-alkylamino-C_1-C_4-alkyl, di-C_1-C_6-alkylamino-C_1-C_4-alkyl, C_3-C_{12}-heterocyclyl-C_1-C_6-alkyl, optionally substituted C_6-C_{12}-aryl or hydroxy. Preferably, R^{12a} is hydrogen or C_1-C_6-alkyl.

R^{13a} is hydrogen, optionally substituted C_1-C_6-alkyl, C_1-C_6-alkylamino-C_1-C_4-alkyl, di-C_1-C_6-alkylamino-C_1-C_4-alkyl, C_3-C_{12}-heterocyclyl-C_1-C_6-alkyl, optionally substituted C_6-C_{12}-aryl or hydroxy. Preferably, R^{13a} is hydrogen or C_1-C_6-alkyl.

In connection with R^{12a} and R^{13a}, substituted C_1-C_6-alkyl in particular includes C_1-C_6-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^{13a}, substituted C_6-C_{12}-aryl in particular includes C_6-C_{12}-aryl, such as phenyl, substituted with 1, 2 or 3 substituents selected from the group consisting of C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, C_1-C_4-alkoxy and C_1-C_4-haloalkoxy.

R^{12b} is hydrogen or C_1-C_6-alkyl. According to a particular embodiment, R^{12b} is hydrogen.

R^{13b} is hydrogen or C_1-C_6-alkyl. According to a particular embodiment, R^{13b} is hydrogen.

Alternatively, R^{12a} and R^{12b}, or R^{13a} and R^{13b}, together are together are carbonyl or, preferably, optionally substituted C_1-C_4-alkylene (e.g. 1,3-propylene), wherein one -CH_2- of C_1-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_1-C_4-alkylene in particular includes C_1-C_4-alkylene substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, cyano, C_1-C_4-alkoxy and C_1-C_4-haloalkoxy.

According to a particular embodiment, R^{12a} is C_1-C_6-alkyl and R^{12b} is hydrogen or C_1-C_6-alkyl, or R^{13a} is C_1-C_6-alkyl and R^{13b} is hydrogen or C_1-C_6-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 C_6-C_{12}-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 C_3-C_{12}-cycloalkyl (e.g. cyclohexyl) or optionally substituted C_3-C_{12}-heterocyclyl.

In connection with R^5, substituted C_3-C_{12}-cycloalkyl in particular includes C_3-C_{12}-cycloalkyl, such as cyclopropyl or cyclohexyl, substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, optionally substituted C_1-C_6-alkyl, halogenated C_1-C_6-alkyl,

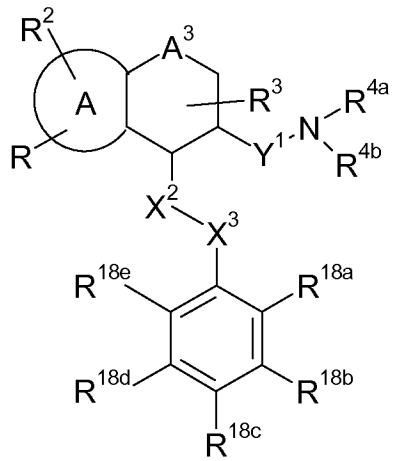
CN, hydroxy, C_1-C_6-alkoxy, halogenated C_1-C_6-alkoxy, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino and C_3-C_{12}-heterocyclyl.

In connection with R^5, substituted C_6-C_{12}-aryl in particular includes C_6-C_{12}-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 C_1-C_6-alkyl (e.g. methyl), halogenated C_1-C_6-alkyl (e.g. trifluoromethyl), CN, hydroxy, C_1-C_6-alkoxy (e.g. methoxy), halogenated C_1-C_6-alkoxy, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino and C_3-C_{12}-heterocyclyl.

In connection with R^5, substituted C_3-C_{12}-heterocyclyl in particular includes C_3-C_{12}-heterocyclyl substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, optionally substituted C_1-C_6-alkyl, halogenated C_1-C_6-alkyl, CN, hydroxy, C_1-C_6-alkoxy, halogenated C_1-C_6-alkoxy, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino and C_3-C_{12}-heterocyclyl.

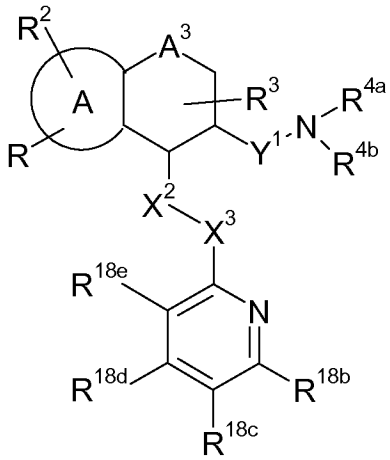
In connection with R^5, C_3-C_{12}-heterocyclyl in particular is C_3-C_{12}-heteroaryl.

Preferably, R^5 is optionally substituted C_6-C_{12}-aryl, in particular as in the compounds of the formula:



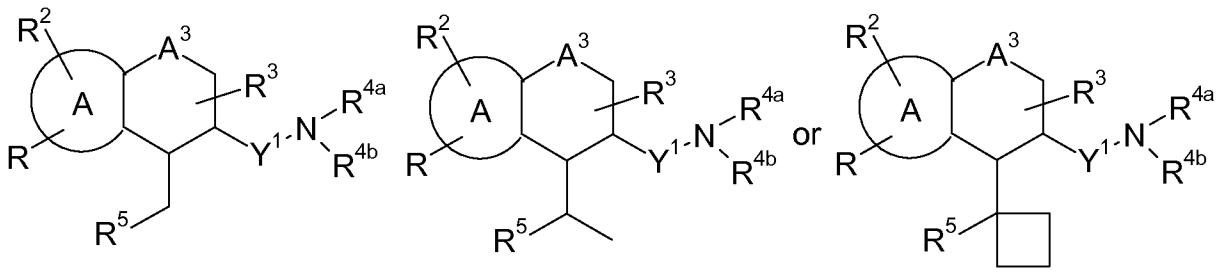
wherein A, R, R^2, A^3, R^3, Y^1, R^{4a}, R^{4b}, X^2, X^3 are as defined herein, and R^{18a}, R^{18b}, R^{18c}, R^{18d}, R^{18e} independently are hydrogen, halogen (e.g. F, Cl or Br), optionally substituted C_1-C_6-alkyl (e.g. methyl), halogenated C_1-C_6-alkyl (e.g. trifluoromethyl), CN, hydroxy, C_1-C_6-alkoxy (e.g. methoxy), amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino or C_3-C_{12}-heterocyclyl.

It is also prefered if R^5 is optionally substituted C_6-C_{12}-heteroaryl, in particular as in the compounds of the formula:



wherein A, R, R^2, A^3, R^3, Y^1, R^{4a}, R^{4b}, X^2, X^3 are as defined herein, and R^{18b}, R^{18c}, R^{18d}, R^{18e} independently are hydrogen, halogen (e.g. F, Cl or Br), optionally substituted C_1-C_6-alkyl (e.g. methyl), halogenated C_1-C_6-alkyl (e.g. trifluoromethyl), CN, hydroxy, C_1-C_6-alkoxy (e.g. methoxy), amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino or C_3-C_{12}-heterocyclyl.

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



wherein A, R, R^2, A^3, R^3, Y^1, R^{4a}, R^{4b},R^5 are as defined herein, R^5 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 R^5 or R^{18a}, R^{18b}, R^{18c}, R^{18d}, R^{18e}, substituted C_1-C_6-alkyl in particular includes C_1-C_6-alkyl, especially C_1-C_4-alkyl, substituted with 1, 2 or 3 substituents selected from the group consisting of hydroxy, C_1-C_6-alkoxy, amino, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino and C_3-C_{12}-heterocyclyl (e.g. morpholinyl or piperidinyl).

According to a particular embodiment, R^{18a}, R^{18b}, R^{18d}, R^{18e} are hydrogen and R^{18c} is different from hydrogen (para-mono-substitution).

According to a further particular embodiment, R^{18a}, R^{18c}, R^{18d}, R^{18e} are hydrogen and R^{18b} is different from hydrogen (meta-mono-substitution).

In connection with R^{18a}, R^{18b}, R^{18c}, R^{18d}, R^{18e}, C_3-C_{12}-heterocyclyl in particular includes morpholinyl, imidazolyl and pyrazolyl.

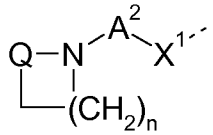
R^6 is hydrogen or C_1-C_6-alkyl. Preferably, R^6 is hydrogen.

R^7 is hydrogen or C_1-C_6-alkyl. Preferably, R^7 is hydrogen.

R^8 is hydrogen or C_1-C_6-alkyl. Preferably, R^8 is hydrogen.

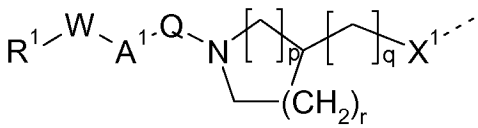
R^9 is hydrogen, C_1-C_6-alkyl (e.g. methyl or ethyl), C_3-C_{12}-cycloalkyl (e.g. cyclopropyl), amino-C_1-C_6-alkyl, optionally substituted C_6-C_{12}-aryl-C_1-C_4-alkyl or C_3-C_{12}-heterocyclyl (e.g. 3-azetidinyl). Preferably, R^9 is hydrogen or C_1-C_6-alkyl (e.g. methyl or ethyl).

According to a particular embodiment, R^9 and R^1 together are C_1-C_4-alkylene (e.g. 1,3-1,2-ethylene or propylene) so as that R^9 and R^1 together with the atom in Q to which R^1 is bound and the nitrogen atom to which R^9 is bound form an heterocyclic ring having, in particular, 4, 5 or 6 ring member atoms (including the nitrogen atom and Q). With W and A^1 both being a bond, such a ring may be represented by the following partial structure:



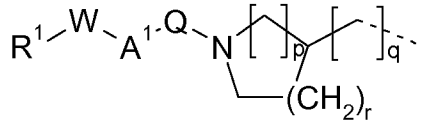
wherein Q, A^2, X^1, are as defined herein (e.g. $S(O)_2$) and n is 0, 1, 2, 3 or 4.

According to a further particular embodiment, R^9 is C_1-C_4-alkylene (e.g. methylene or 1,3-propylene) that is bound to a carbon atom in A^2 and A^2 is C_1-C_4-alkylene so that R^9 and at least part of A^2 together with the nitrogen atom to which R^9 is bound form an N-containing heterocyclic ring having, in particular, 4, 5, 6 or 7 ring member atoms (including the nitrogen atom). Such a ring may be represented by the following partial structure:



wherein R^1, W, A^1, Q and X^1 are as defined herein, p is 1 or 2, r is 0, 1 or 2 and q is 0, 1 or 2. In this particular embodiment, X^1 preferably is -O-. Particular combinations of p, r and q include p=1, r=0, q=1; and p=1, r=0, q=0. Alternatively, p is 0, r is 3 and q is 1, with X^1 preferably being -O-.

According to a further particular embodiment, R^9 is C_1-C_4-alkylene (e.g. methylene or 1,3-propylene) that is bound to a carbon atom in X^1 and X^1 is C_1-C_4-alkylene (e.g. 1,2-ethylene) so that R^9 and at least part of X^1 together with the nitrogen atom to which R^9 is bound form an N-containing heterocyclic ring having, in particular, 4, 5, 6 or 7 ring member atoms (including the nitrogen atom). With A^2 being a bond, such a ring may be represented by the following partial structure:



wherein R^1, W, A^1 and Q are as defined herein, p is 1 or 2, r is 0, 1 or 2 and q is 0, 1 or 2. Particular combinations of p, r and q include p=1, r=0, q=0.

R^{10} is hydrogen, C_1-C_6-alkyl or C_1-C_6-alkylsulfonyl. Preferably, R^{10} is hydrogen.

R^{11} is hydrogen or C_1-C_6-alkyl. Preferably, R^{11} is hydrogen.

Alternatively, R^9, R^{11} together are C_1-C_4-alkylene (e.g. ethylene).

R^{14} is hydrogen or C_1-C_6-alkyl. Preferably, R^{14} is hydrogen.

R^{15} is hydrogen or C_1-C_6-alkyl. Preferably, R^{15} is hydrogen.

R^{16} is hydrogen, C_1-C_6-alkyl, C_3-C_{12}-cycloalkyl-C_1-C_4-alkyl, halogenated C_1-C_4-alkyl, hydroxy-C_1-C_4-alkyl, C_1-C_6-alkoxy-C_1-C_4-alkyl, amino-C_1-C_4-alkyl, CH_2CN, C_6-C_{12}-aryl-C_1-C_4-alkyl, C_3-C_{12}-cycloalkyl, -CHO, C_1-C_4-alkylcarbonyl, (halogenated C_1-C_4-alkyl)carbonyl, C_6-C_{12}-arylcarbonyl, C_1-C_4-alkoxycarbonyl, C_6-C_{12}-aryloxycarbonyl, C_1-C_6-alkylaminocarbonyl, C_2-C_6-alkenyl, -C(=NH)NH_2, -C(=NH)NHCN, C_1-C_6-alkylsulfonyl, C_6-C_{12}-arylsulfonyl, amino, -NO or C_3-C_{12}-heterocyclyl. Preferably, R^{16} is hydrogen.

R^{17} is hydrogen or C_1-C_6-alkyl. Preferably, R^{17} is hydrogen.

Particular embodiments of compounds of the invention result if

A is a benzene ring;

R is R^1-W-A^1-Q-Y-A^2-X^1-;

R^1 is C_1-C_6-alkyl (e.g. ethyl, n-propyl, isopropyl, 2-butyl), C_3-C_{12}-cycloalkyl-C_1-C_4-alkyl (e.g. cyclopropylmethyl), C_3-C_{12}-cycloalkyl (e.g. cyclobutyl), or optionally substituted C_3-C_{12}-heterocyclyl (e.g. 3-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, 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);

W is a bond;

A^1 is a bond;

Q is $-S(O)_2-$;

Y is $-NR^9-$ or a bond;

A^2 is C_1-C_4-alkylene (e.g. 1,2-ethylene) or a bond;

X^1 is -O- or optionally substituted C_1-C_4-alkylene (e.g. methylene, 1,2-ethylene);

R^2 is hydrogen or halogen (e.g. fluorine);

A^3 is -O-;

R^3 is hydrogen or C_1-C_6-alkyl (e.g. methyl);

Y^1 is a bond;

R^{4a} is hydrogen, C_1-C_6-alkyl (e.g. methyl, ethyl, n-propyl, 2-methyl-but-4-yl, 2-methyl-prop-3-yl), C_3-C_{12}-cycloalkyl (e.g. cyclopropyl) or C_3-C_{12}-cycloalkyl-C_1-C_4-alkyl (e.g. cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, 1-cyclopropyleth-2-yl, 1-cyclopentyleth-2-yl, or cyclohexylmethyl);

R^{4b} is hydrogen; or

R^{4a}, R^{4b} together are C_1-C_6-alkylene (e.g. 1,3-propylene, 1,4-butylene);

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

X^3 is a bond;

R^5 is optionally substituted phenyl (e.g. phenyl, 2-fluorophenyl, 2-chlorophenyl, 3-fluorophenyl, 3-chlorophenyl, 3-trifluoromethylphenyl);

R^9 is hydrogen, or

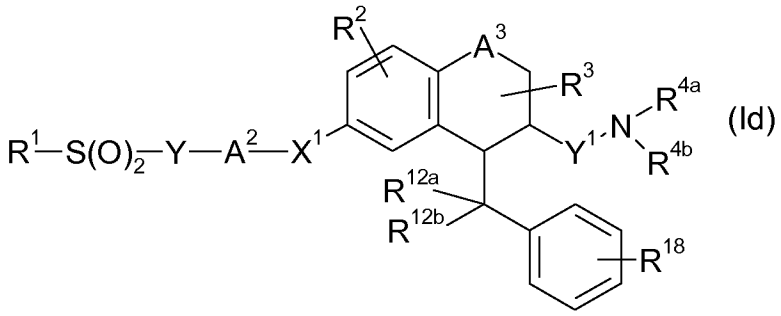
R^9 is C_1-C_4-alkylene (e.g. methylene) that is bound to a carbon atom in X^1 and X^1 is C_1-C_4-alkylene (e.g. 1,2-ethylene);

R^{12a} is hydrogen or C_1-C_6-alkyl;

R^{12b} is hydrogen; or

R^{12a}, R^{12b} together are C_1-C_4-alkylene (e.g. 1,3-propylene).

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:



(Id)

Table 1

Compounds of the formula (Id) wherein -A^3- 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^{18} is hydrogen and the combination of R^1, -Y-A^2-X^1-, >$CR^{12a}R^{12b}$, R^{4a}, R^{4b} for a compound in each case corresponds to one line of Table A (A-1 to A-540).

Table 2

Compounds of the formula (Id) wherein -A^3- 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^{18} is 3-F and the combination of R^1, -Y-A^2-X^1-, >$CR^{12a}R^{12b}$, R^{4a}, R^{4b} for a compound in each case corresponds to one line of Table A (A-1 to A-540).

Table 3

Compounds of the formula (Id) wherein -A^3- 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^{18} is 3-Cl and the combination of R^1, -Y-A^2-X^1-, >$CR^{12a}R^{12b}$, R^{4a}, R^{4b} for a compound in each case corresponds to one line of Table A (A-1 to A-540).

Table 4

Compounds of the formula (Id) wherein -A^3- 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^{18} is 3-CF_3 and the combination of R^1, -Y-A^2-X^1-, >$CR^{12a}R^{12b}$, R^{4a}, R^{4b} for a compound in each case corresponds to one line of Table A (A-1 to A-540).

Table 5

Compounds of the formula (Id) wherein -A^3- 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^{18} is 4-F and the combina-

tion of R^1, -Y-A^2-X^1-, >$CR^{12a}R^{12b}$, R^{4a}, R^{4b} for a compound in each case corresponds to one line of Table A (A-1 to A-540).

Table 6

Compounds of the formula (Id) wherein -A^3- 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^{18} is 4-Cl and the combination of R^1, -Y-A^2-X^1-, >$CR^{12a}R^{12b}$, R^{4a}, R^{4b} for a compound in each case corresponds to one line of Table A (A-1 to A-540).

Table 7

Compounds of the formula (Id) wherein -A^3- 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^{18} is hydrogen and the combination of R^1, -Y-A^2-X^1-, >$CR^{12a}R^{12b}$, R^{4a}, R^{4b} for a compound in each case corresponds to one line of Table A (A-1 to A-540).

Table 8

Compounds of the formula (Id) wherein -A^3- 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^{18} is 3-F and the combination of R^1, -Y-A^2-X^1-, >$CR^{12a}R^{12b}$, R^{4a}, R^{4b} for a compound in each case corresponds to one line of Table A (A-1 to A-540).

Table 9

Compounds of the formula (Id) wherein -A^3- 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^{18} is 3-Cl and the combination of R^1, -Y-A^2-X^1-, >$CR^{12a}R^{12b}$, R^{4a}, R^{4b} for a compound in each case corresponds to one line of Table A (A-1 to A-540).

Table 10

Compounds of the formula (Id) wherein -A^3- 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^{18} is 3-CF_3 and the combination of R^1, -Y-A^2-X^1-, >$CR^{12a}R^{12b}$, R^{4a}, R^{4b} for a compound in each case corresponds to one line of Table A (A-1 to A-540).

Table 11

Compounds of the formula (Id) wherein -A^3- 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^{18} is 4-F and the combination of R^1, -Y-A^2-X^1-, >$CR^{12a}R^{12b}$, R^{4a}, R^{4b} for a compound in each case corresponds to one line of Table A (A-1 to A-540).

Table 12
Compounds of the formula (Id) wherein -A^3- 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^{18} is 4-Cl and the combination of R^1, -Y-A^2-X^1-, >$CR^{12a}R^{12b}$, R^{4a}, R^{4b} for a compound in each case corresponds to one line of Table A (A-1 to A-540).

Table 13
Compounds of the formula (Id) wherein -A^3- is as defined herein and in particular represents –O-, -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^{18} is hydrogen and the combination of R^1, -Y-A^2-X^1-, >$CR^{12a}R^{12b}$, R^{4a}, R^{4b} for a compound in each case corresponds to one line of Table A (A-1 to A-540).

Table 14
Compounds of the formula (Id) wherein -A^3- is as defined herein and in particular represents –O-, -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^{18} is 3-F and the combination of R^1, -Y-A^2-X^1-, >$CR^{12a}R^{12b}$, R^{4a}, R^{4b} for a compound in each case corresponds to one line of Table A (A-1 to A-540).

Table 15
Compounds of the formula (Id) wherein -A^3- is as defined herein and in particular represents –O-, -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^{18} is 3-Cl and the combination of R^1, -Y-A^2-X^1-, >$CR^{12a}R^{12b}$, R^{4a}, R^{4b} for a compound in each case corresponds to one line of Table A (A-1 to A-540).

Table 16
Compounds of the formula (Id) wherein -A^3- is as defined herein and in particular represents –O-, -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^{18} is 3-CF_3 and the combination of R^1, -Y-A^2-X^1-, >$CR^{12a}R^{12b}$, R^{4a}, R^{4b} for a compound in each case corresponds to one line of Table A (A-1 to A-540).

Table 17
Compounds of the formula (Id) wherein -A^3- is as defined herein and in particular repre-

sents –O-, -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^{18} is 4-F and the combination of R^1, -Y-A^2-X^1-, >$CR^{12a}R^{12b}$, R^{4a}, R^{4b} for a compound in each case corresponds to one line of Table A (A-1 to A-540).

Table 18

Compounds of the formula (Id) wherein -A^3- is as defined herein and in particular represents –O-, -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^{18} is 4-Cl and the combination of R^1, -Y-A^2-X^1-, >$CR^{12a}R^{12b}$, R^{4a}, R^{4b} for a compound in each case corresponds to one line of Table A (A-1 to A-540).

Table 19

Compounds of the formula (Id) wherein -A^3- is as defined herein and in particular represents –O-, -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^{18} is hydrogen and the combination of R^1, -Y-A^2-X^1-, >$CR^{12a}R^{12b}$, R^{4a}, R^{4b} for a compound in each case corresponds to one line of Table A (A-1 to A-540).

Table 20

Compounds of the formula (Id) wherein -A^3- is as defined herein and in particular represents –O-, -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^{18} is 3-F and the combination of R^1, -Y-A^2-X^1-, >$CR^{12a}R^{12b}$, R^{4a}, R^{4b} for a compound in each case corresponds to one line of Table A (A-1 to A-540).

Table 21

Compounds of the formula (Id) wherein -A^3- is as defined herein and in particular represents –O-, -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^{18} is 3-Cl and the combination of R^1, -Y-A^2-X^1-, >$CR^{12a}R^{12b}$, R^{4a}, R^{4b} for a compound in each case corresponds to one line of Table A (A-1 to A-540).

Table 22

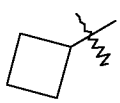
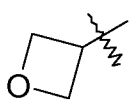
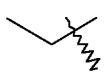
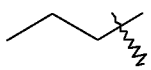
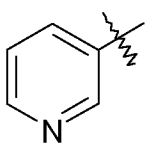
Compounds of the formula (Id) wherein -A^3- is as defined herein and in particular represents –O-, -Y^1- is as defined herein and in particular represents a bond, R^2 is 8-F, R^3 is as defined herein and in particular represents hydrogen, R^{18} is 3-CF_3 and the combination of R^1, -Y-A^2-X^1-, >$CR^{12a}R^{12b}$, R^{4a}, R^{4b} for a compound in each case corresponds to one line of Table A (A-1 to A-540).

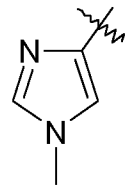
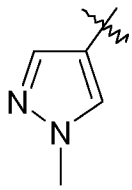
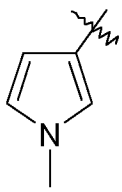
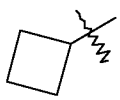
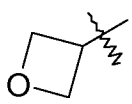
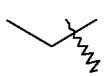
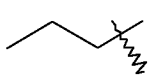
Table 23

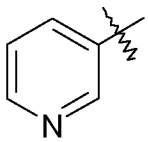
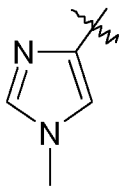
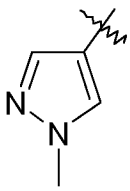
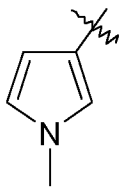
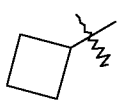
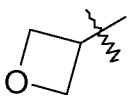
Compounds of the formula (Id) wherein -A^3- is as defined herein and in particular represents –O-, -Y^1- is as defined herein and in particular represents a bond, R^2 is 8-F, R^3 is as defined herein and in particular represents hydrogen, R^{18} is 4-F and the combination of R^1, -Y-A^2-X^1-, >$CR^{12a}R^{12b}$, R^{4a}, R^{4b} for a compound in each case corresponds to one line of Table A (A-1 to A-540).

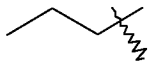
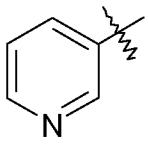
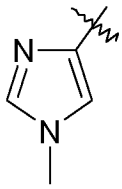
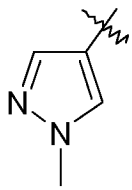
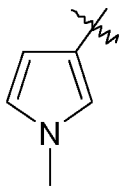
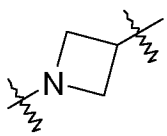
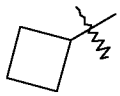
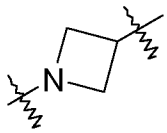
Table 24

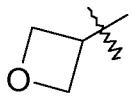
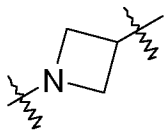
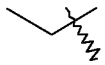
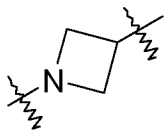
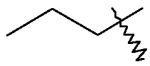
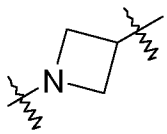
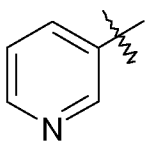
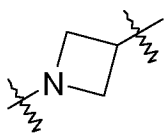
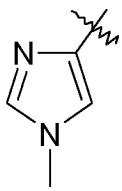
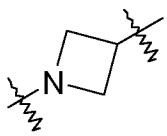
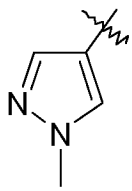
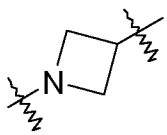
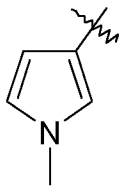
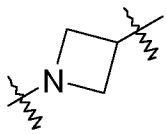
Compounds of the formula (Id) wherein -A^3- is as defined herein and in particular represents –O-, -Y^1- is as defined herein and in particular represents a bond, R^2 is 8-F, R^3 is as defined herein and in particular represents hydrogen, R^{18} is 4-Cl and the combination of R^1, -Y-A^2-X^1-, >$CR^{12a}R^{12b}$, R^{4a}, R^{4b} for a compound in each case corresponds to one line of Table A (A-1 to A-540).

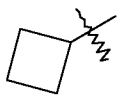
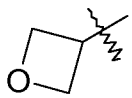
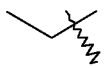
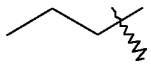
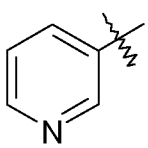
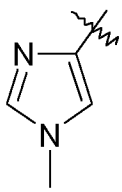
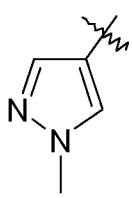
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-1.		-NH-$(CH_2)_2$-O-	-CH_2-	H, H
A-2.		-NH-$(CH_2)_2$-O-	-CH_2-	H, H
A-3.		-NH-$(CH_2)_2$-O-	-CH_2-	H, H
A-4.		-NH-$(CH_2)_2$-O-	-CH_2-	H, H
A-5.		-NH-$(CH_2)_2$-O-	-CH_2-	H, H
A-6.		-NH-$(CH_2)_2$-O-	-CH_2-	H, H

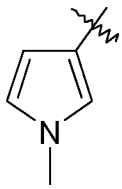
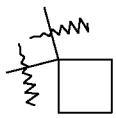
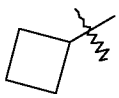
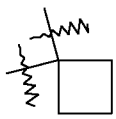
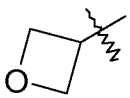
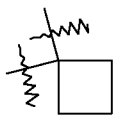
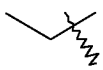
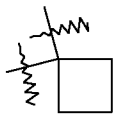
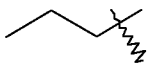
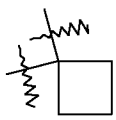
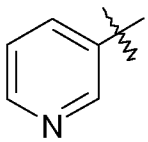
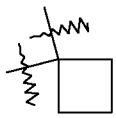
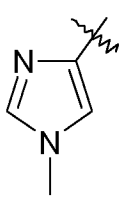
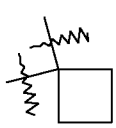
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-7.		-NH-$(CH_2)_2$-O-	-CH_2-	H, H
A-8.		-NH-$(CH_2)_2$-O-	-CH_2-	H, H
A-9.		-NH-$(CH_2)_2$-O-	-CH_2-	H, H
A-10.		-NH-$(CH_2)_2$-	-CH_2-	H, H
A-11.		-NH-$(CH_2)_2$-	-CH_2-	H, H
A-12.		-NH-$(CH_2)_2$-	-CH_2-	H, H
A-13.		-NH-$(CH_2)_2$-	-CH_2-	H, H
A-14.		-NH-$(CH_2)_2$-	-CH_2-	H, H

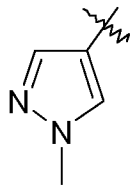
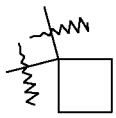
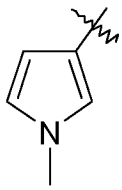
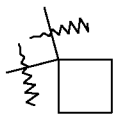
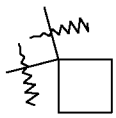
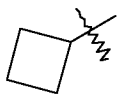
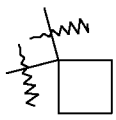
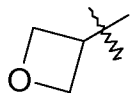
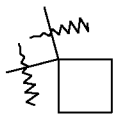
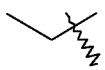
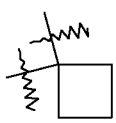
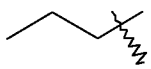
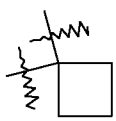
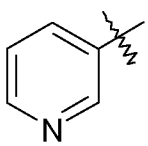
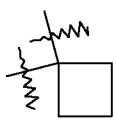
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-15.		$-NH-(CH_2)_2-$	$-CH_2-$	H, H
A-16.		$-NH-(CH_2)_2-$	$-CH_2-$	H, H
A-17.		$-NH-(CH_2)_2-$	$-CH_2-$	H, H
A-18.		$-NH-(CH_2)_2-$	$-CH_2-$	H, H
A-19.		$-NH-CH_2-$	$-CH_2-$	H, H
A-20.		$-NH-CH_2-$	$-CH_2-$	H, H
A-21.		$-NH-CH_2-$	$-CH_2-$	H, H
A-22.		$-NH-CH_2-$	$-CH_2-$	H, H

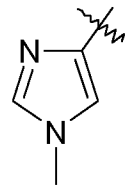
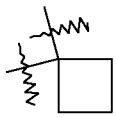
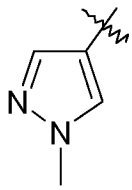
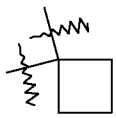
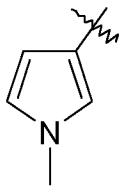
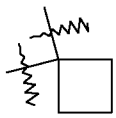
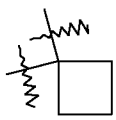
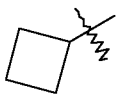
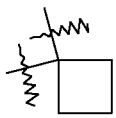
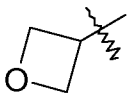
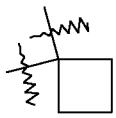
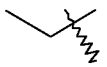
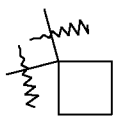
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-23.		-NH-CH_2-	-CH_2-	H, H
A-24.		-NH-CH_2-	-CH_2-	H, H
A-25.		-NH-CH_2-	-CH_2-	H, H
A-26.		-NH-CH_2-	-CH_2-	H, H
A-27.		-NH-CH_2-	-CH_2-	H, H
A-28.			-CH_2-	H, H
A-29.			-CH_2-	H, H

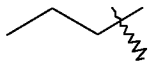
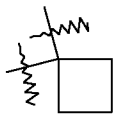
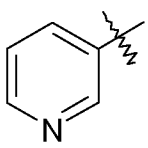
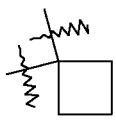
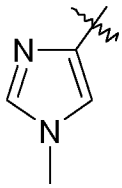
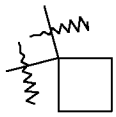
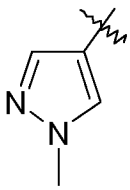
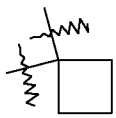
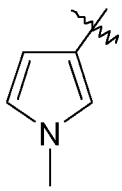
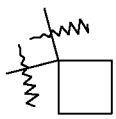
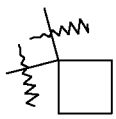
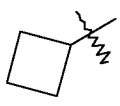
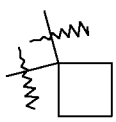
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-30.			$-CH_2-$	H, H
A-31.			$-CH_2-$	H, H
A-32.			$-CH_2-$	H, H
A-33.			$-CH_2-$	H, H
A-34.			$-CH_2-$	H, H
A-35.			$-CH_2-$	H, H
A-36.			$-CH_2-$	H, H

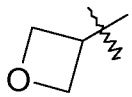
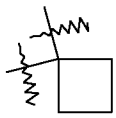
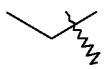
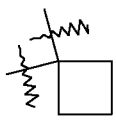
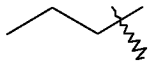
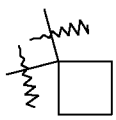
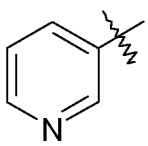
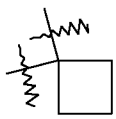
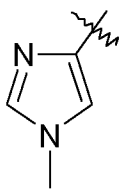
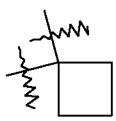
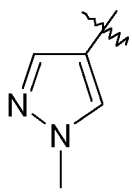
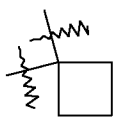
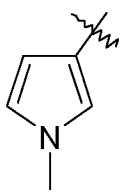
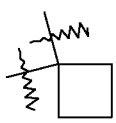
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-37.		-$(CH_2)_2$-	-CH_2-	H, H
A-38.		-$(CH_2)_2$-	-CH_2-	H, H
A-39.		-$(CH_2)_2$-	-CH_2-	H, H
A-40.		-$(CH_2)_2$-	-CH_2-	H, H
A-41.		-$(CH_2)_2$-	-CH_2-	H, H
A-42.		-$(CH_2)_2$-	-CH_2-	H, H
A-43.		-$(CH_2)_2$-	-CH_2-	H, H
A-44.		-$(CH_2)_2$-	-CH_2-	H, H

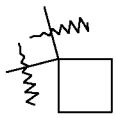
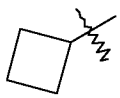
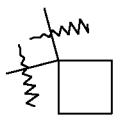
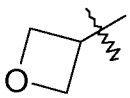
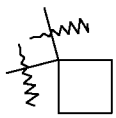
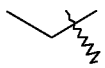
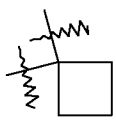
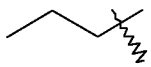
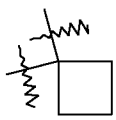
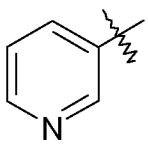
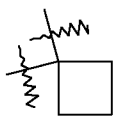
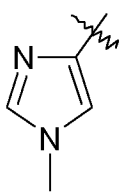
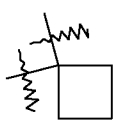
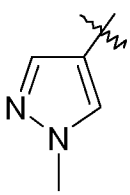
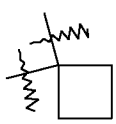
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-45.		-$(CH_2)_2$-	-CH_2-	H, H
A-46.		-NH-$(CH_2)_2$-O-		H, H
A-47.		-NH-$(CH_2)_2$-O-		H, H
A-48.		-NH-$(CH_2)_2$-O-		H, H
A-49.		-NH-$(CH_2)_2$-O-		H, H
A-50.		-NH-$(CH_2)_2$-O-		H, H
A-51.		-NH-$(CH_2)_2$-O-		H, H
A-52.		-NH-$(CH_2)_2$-O-		H, H

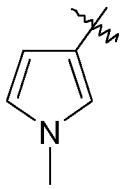
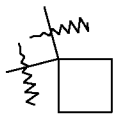
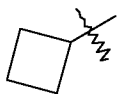
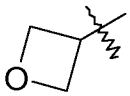
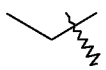
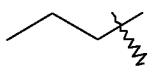
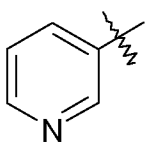
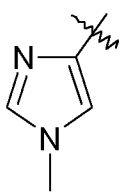
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-53.		$-NH-(CH_2)_2-O-$		H, H
A-54.		$-NH-(CH_2)_2-O-$		H, H
A-55.		$-NH-(CH_2)_2-$		H, H
A-56.		$-NH-(CH_2)_2-$		H, H
A-57.		$-NH-(CH_2)_2-$		H, H
A-58.		$-NH-(CH_2)_2-$		H, H
A-59.		$-NH-(CH_2)_2-$		H, H
A-60.		$-NH-(CH_2)_2-$		H, H

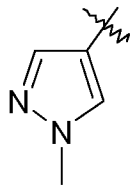
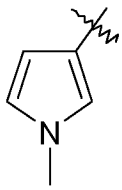
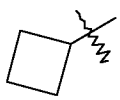
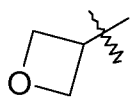
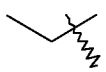
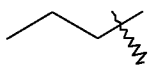
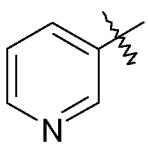
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-61.		-NH-$(CH_2)_2$-		H, H
A-62.		-NH-$(CH_2)_2$-		H, H
A-63.		-NH-$(CH_2)_2$-		H, H
A-64.		-NH-CH_2-		H, H
A-65.		-NH-CH_2-		H, H
A-66.		-NH-CH_2-		H, H
A-67.		-NH-CH_2-		H, H

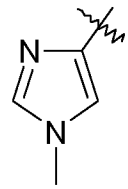
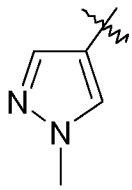
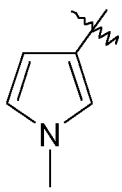
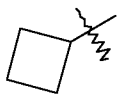
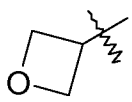
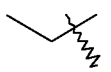
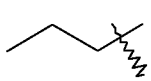
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-68.		$-NH-CH_2-$		H, H
A-69.		$-NH-CH_2-$		H, H
A-70.		$-NH-CH_2-$		H, H
A-71.		$-NH-CH_2-$		H, H
A-72.		$-NH-CH_2-$		H, H
A-73.		$-NH-(CH_2)_3-$		H, H
A-74.		$-NH-(CH_2)_3-$		H, H

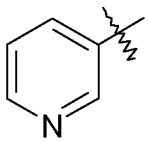
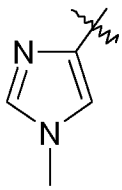
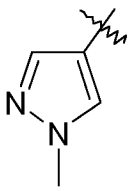
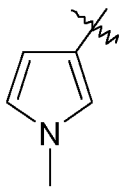
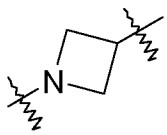
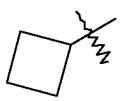
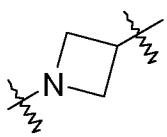
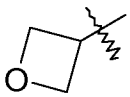
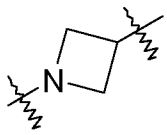
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-75.		-NH-$(CH_2)_3$-		H, H
A-76.		-NH-$(CH_2)_3$-		H, H
A-77.		-NH-$(CH_2)_3$-		H, H
A-78.		-NH-$(CH_2)_3$-		H, H
A-79.		-NH-$(CH_2)_3$-		H, H
A-80.		-NH-$(CH_2)_3$-		H, H
A-81.		-NH-$(CH_2)_3$-		H, H

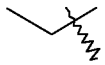
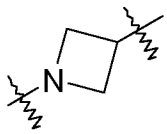
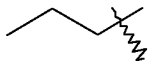
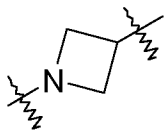
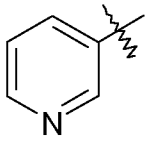
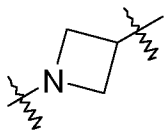
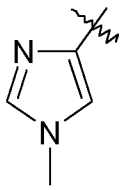
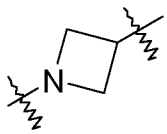
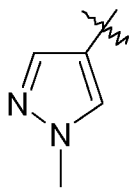
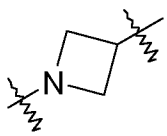
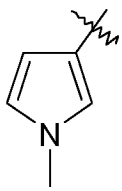
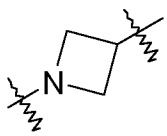
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-82.		-$(CH_2)_2$-		H, H
A-83.		-$(CH_2)_2$-		H, H
A-84.		-$(CH_2)_2$-		H, H
A-85.		-$(CH_2)_2$-		H, H
A-86.		-$(CH_2)_2$-		H, H
A-87.		-$(CH_2)_2$-		H, H
A-88.		-$(CH_2)_2$-		H, H
A-89.		-$(CH_2)_2$-		H, H

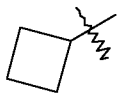
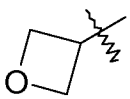
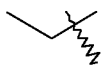
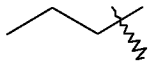
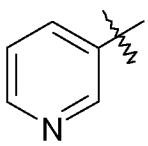
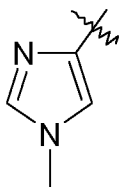
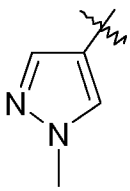
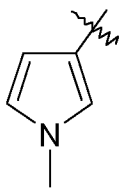
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-90.		$-(CH_2)_2-$		H, H
A-91.		$-NH-(CH_2)_2-O-$	$-CH_2-$	$-CH_3$, H
A-92.		$-NH-(CH_2)_2-O-$	$-CH_2-$	$-CH_3$, H
A-93.		$-NH-(CH_2)_2-O-$	$-CH_2-$	$-CH_3$, H
A-94.		$-NH-(CH_2)_2-O-$	$-CH_2-$	$-CH_3$, H
A-95.		$-NH-(CH_2)_2-O-$	$-CH_2-$	$-CH_3$, H
A-96.		$-NH-(CH_2)_2-O-$	$-CH_2-$	$-CH_3$, H
A-97.		$-NH-(CH_2)_2-O-$	$-CH_2-$	$-CH_3$, H

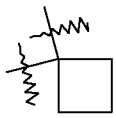
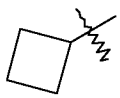
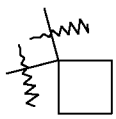
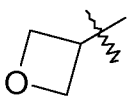
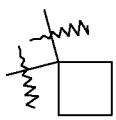
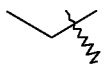
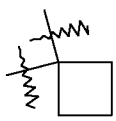
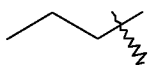
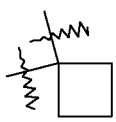
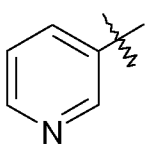
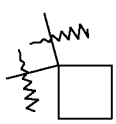
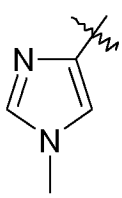
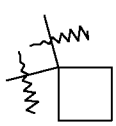
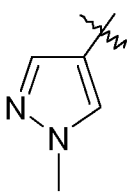
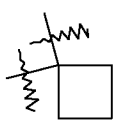
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-98.		-NH-$(CH_2)_2$-O-	-CH_2-	-CH_3, H
A-99.		-NH-$(CH_2)_2$-O-	-CH_2-	-CH_3, H
A-100.		-NH-$(CH_2)_2$-	-CH_2-	-CH_3, H
A-101.		-NH-$(CH_2)_2$-	-CH_2-	-CH_3, H
A-102.		-NH-$(CH_2)_2$-	-CH_2-	-CH_3, H
A-103.		-NH-$(CH_2)_2$-	-CH_2-	-CH_3, H
A-104.		-NH-$(CH_2)_2$-	-CH_2-	-CH_3, H
A-105.		-NH-$(CH_2)_2$-	-CH_2-	-CH_3, H

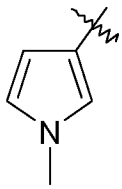
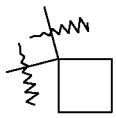
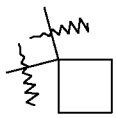
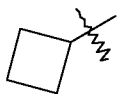
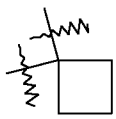
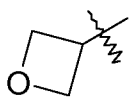
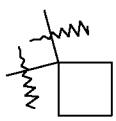
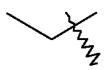
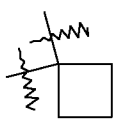
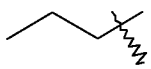
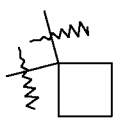
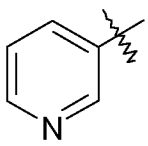
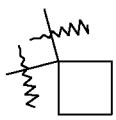
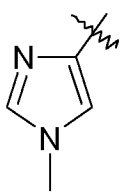
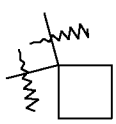
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-106.		-NH-$(CH_2)_2$-	-CH_2-	-CH_3, H
A-107.		-NH-$(CH_2)_2$-	-CH_2-	-CH_3, H
A-108.		-NH-$(CH_2)_2$-	-CH_2-	-CH_3, H
A-109.		-NH-CH_2-	-CH_2-	-CH_3, H
A-110.		-NH-CH_2-	-CH_2-	-CH_3, H
A-111.		-NH-CH_2-	-CH_2-	-CH_3, H
A-112.		-NH-CH_2-	-CH_2-	-CH_3, H
A-113.		-NH-CH_2-	-CH_2-	-CH_3, H

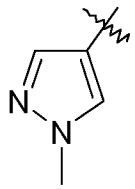
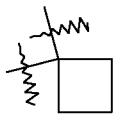
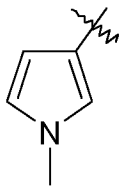
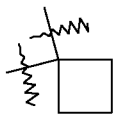
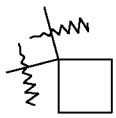
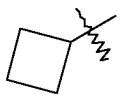
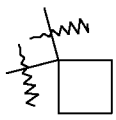
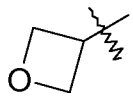
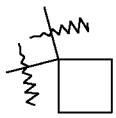
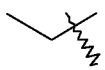
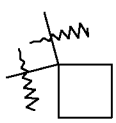
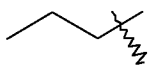
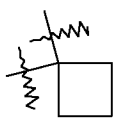
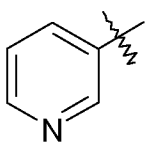
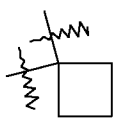
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-114.		-NH-CH_2-	-CH_2-	-CH_3, H
A-115.		-NH-CH_2-	-CH_2-	-CH_3, H
A-116.		-NH-CH_2-	-CH_2-	-CH_3, H
A-117.		-NH-CH_2-	-CH_2-	-CH_3, H
A-118.			-CH_2-	-CH_3, H
A-119.			-CH_2-	-CH_3, H
A-120.			-CH_2-	-CH_3, H

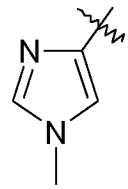
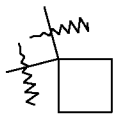
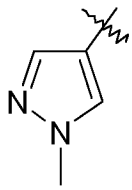
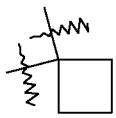
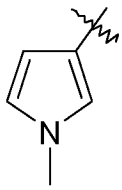
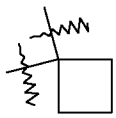
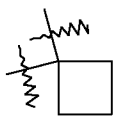
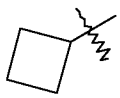
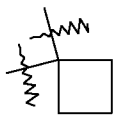
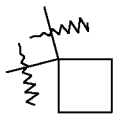
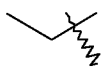
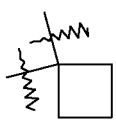
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-121.			$-CH_2-$	$-CH_3$, H
A-122.			$-CH_2-$	$-CH_3$, H
A-123.			$-CH_2-$	$-CH_3$, H
A-124.			$-CH_2-$	$-CH_3$, H
A-125.			$-CH_2-$	$-CH_3$, H
A-126.			$-CH_2-$	$-CH_3$, H
A-127.		$-(CH_2)_2-$	$-CH_2-$	$-CH_3$, H

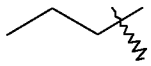
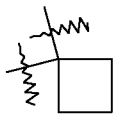
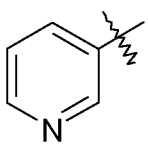
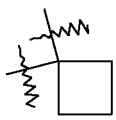
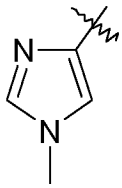
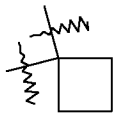
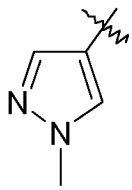
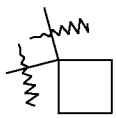
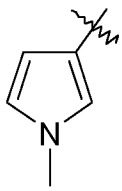
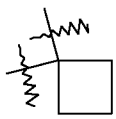
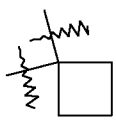
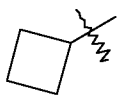
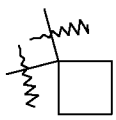
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-128.		-$(CH_2)_2$-	-CH_2-	-CH_3, H
A-129.		-$(CH_2)_2$-	-CH_2-	-CH_3, H
A-130.		-$(CH_2)_2$-	-CH_2-	-CH_3, H
A-131.		-$(CH_2)_2$-	-CH_2-	-CH_3, H
A-132.		-$(CH_2)_2$-	-CH_2-	-CH_3, H
A-133.		-$(CH_2)_2$-	-CH_2-	-CH_3, H
A-134.		-$(CH_2)_2$-	-CH_2-	-CH_3, H
A-135.		-$(CH_2)_2$-	-CH_2-	-CH_3, H

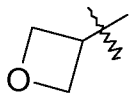
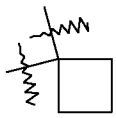
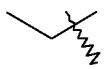
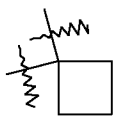
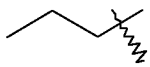
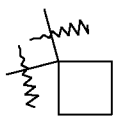
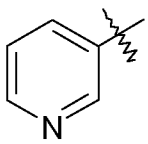
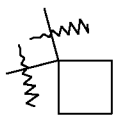
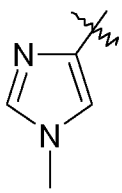
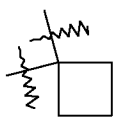
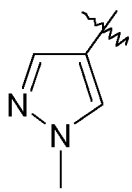
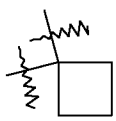
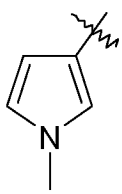
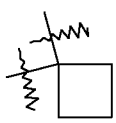
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-136.		-NH-$(CH_2)_2$-O-		-CH_3, H
A-137.		-NH-$(CH_2)_2$-O-		-CH_3, H
A-138.		-NH-$(CH_2)_2$-O-		-CH_3, H
A-139.		-NH-$(CH_2)_2$-O-		-CH_3, H
A-140.		-NH-$(CH_2)_2$-O-		-CH_3, H
A-141.		-NH-$(CH_2)_2$-O-		-CH_3, H
A-142.		-NH-$(CH_2)_2$-O-		-CH_3, H
A-143.		-NH-$(CH_2)_2$-O-		-CH_3, H

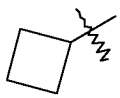
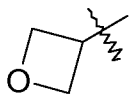
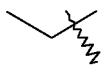
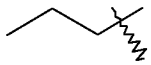
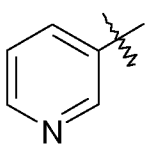
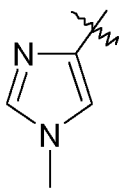
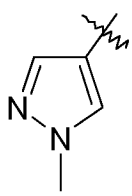
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-144.		-NH-$(CH_2)_2$-O-		-CH_3, H
A-145.		-NH-$(CH_2)_2$-		-CH_3, H
A-146.		-NH-$(CH_2)_2$-		-CH_3, H
A-147.		-NH-$(CH_2)_2$-		-CH_3, H
A-148.		-NH-$(CH_2)_2$-		-CH_3, H
A-149.		-NH-$(CH_2)_2$-		-CH_3, H
A-150.		-NH-$(CH_2)_2$-		-CH_3, H
A-151.		-NH-$(CH_2)_2$-		-CH_3, H

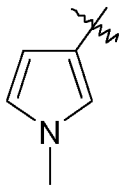
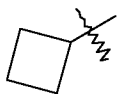
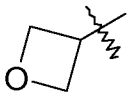
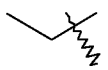
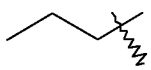
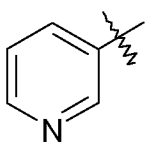
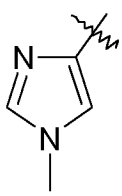
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-152.		$-NH-(CH_2)_2-$		$-CH_3$, H
A-153.		$-NH-(CH_2)_2-$		$-CH_3$, H
A-154.		$-NH-CH_2-$		$-CH_3$, H
A-155.		$-NH-CH_2-$		$-CH_3$, H
A-156.		$-NH-CH_2-$		$-CH_3$, H
A-157.		$-NH-CH_2-$		$-CH_3$, H
A-158.		$-NH-CH_2-$		$-CH_3$, H
A-159.		$-NH-CH_2-$		$-CH_3$, H

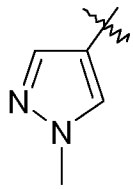
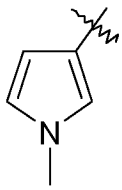
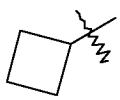
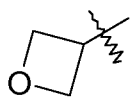
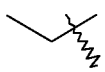
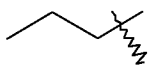
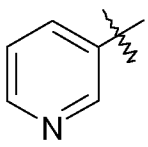
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-160.		$-NH-CH_2-$		$-CH_3$, H
A-161.		$-NH-CH_2-$		$-CH_3$, H
A-162.		$-NH-CH_2-$		$-CH_3$, H
A-163.		$-NH-(CH_2)_3-$		$-CH_3$, H
A-164.		$-NH-(CH_2)_3-$		$-CH_3$, H
A-165.		$-NH-(CH_2)_3-$		$-CH_3$, H
A-166.		$-NH-(CH_2)_3-$		$-CH_3$, H

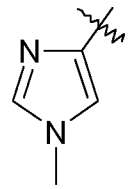
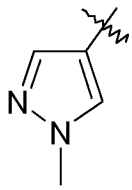
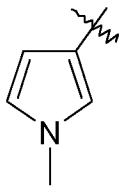
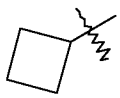
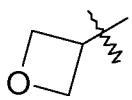
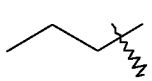
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-167.		-NH-$(CH_2)_3$-		-CH_3, H
A-168.		-NH-$(CH_2)_3$-		-CH_3, H
A-169.		-NH-$(CH_2)_3$-		-CH_3, H
A-170.		-NH-$(CH_2)_3$-		-CH_3, H
A-171.		-NH-$(CH_2)_3$-		-CH_3, H
A-172.		-$(CH_2)_2$-		-CH_3, H
A-173.		-$(CH_2)_2$-		-CH_3, H

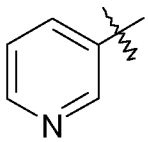
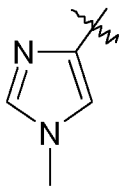
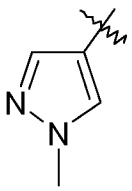
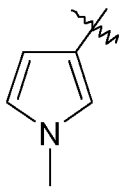
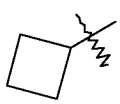
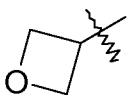
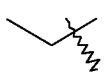
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-174.		$-(CH_2)_2-$		$-CH_3$, H
A-175.		$-(CH_2)_2-$		$-CH_3$, H
A-176.		$-(CH_2)_2-$		$-CH_3$, H
A-177.		$-(CH_2)_2-$		$-CH_3$, H
A-178.		$-(CH_2)_2-$		$-CH_3$, H
A-179.		$-(CH_2)_2-$		$-CH_3$, H
A-180.		$-(CH_2)_2-$		$-CH_2CH_3$, H

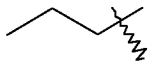
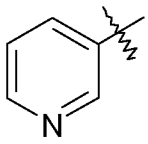
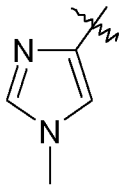
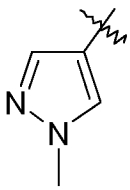
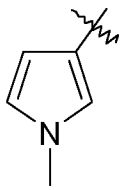
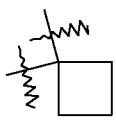
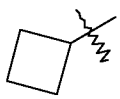
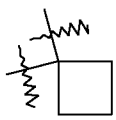
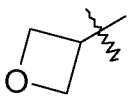
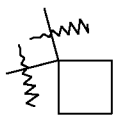
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-181.		-NH-$(CH_2)_2$-O-	-CH_2-	-CH_2CH_3, H
A-182.		-NH-$(CH_2)_2$-O-	-CH_2-	-CH_2CH_3, H
A-183.		-NH-$(CH_2)_2$-O-	-CH_2-	-CH_2CH_3, H
A-184.		-NH-$(CH_2)_2$-O-	-CH_2-	-CH_2CH_3, H
A-185.		-NH-$(CH_2)_2$-O-	-CH_2-	-CH_2CH_3, H
A-186.		-NH-$(CH_2)_2$-O-	-CH_2-	-CH_2CH_3, H
A-187.		-NH-$(CH_2)_2$-O-	-CH_2-	-CH_2CH_3, H
A-188.		-NH-$(CH_2)_2$-O-	-CH_2-	-CH_2CH_3, H

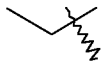
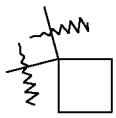
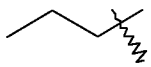
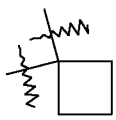
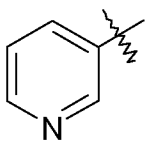
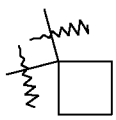
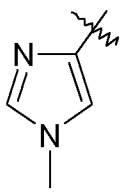
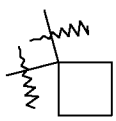
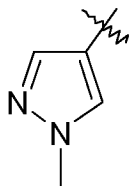
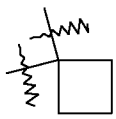
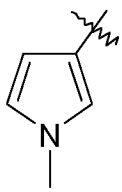
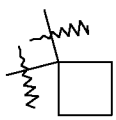
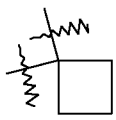
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-189.		-NH-$(CH_2)_2$-O-	-CH_2-	-CH_2CH_3, H
A-190.		-NH-$(CH_2)_2$-	-CH_2-	-CH_2CH_3, H
A-191.		-NH-$(CH_2)_2$-	-CH_2-	-CH_2CH_3, H
A-192.		-NH-$(CH_2)_2$-	-CH_2-	-CH_2CH_3, H
A-193.		-NH-$(CH_2)_2$-	-CH_2-	-CH_2CH_3, H
A-194.		-NH-$(CH_2)_2$-	-CH_2-	-CH_2CH_3, H
A-195.		-NH-$(CH_2)_2$-	-CH_2-	-CH_2CH_3, H
A-196.		-NH-$(CH_2)_2$-	-CH_2-	-CH_2CH_3, H

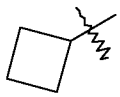
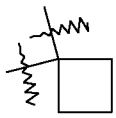
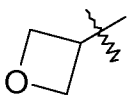
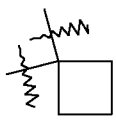
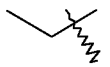
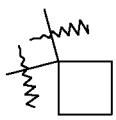
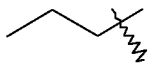
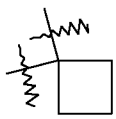
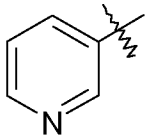
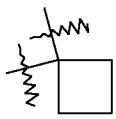
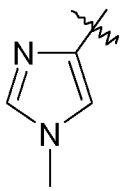
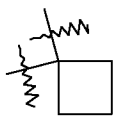
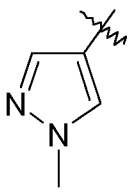
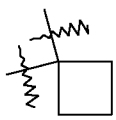
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-197.		-NH-$(CH_2)_2$-	-CH_2-	-CH_2CH_3, H
A-198.		-NH-$(CH_2)_2$-	-CH_2-	-CH_2CH_3, H
A-199.		-NH-CH_2-	-CH_2-	-CH_2CH_3, H
A-200.		-NH-CH_2-	-CH_2-	-CH_2CH_3, H
A-201.		-NH-CH_2-	-CH_2-	-CH_2CH_3, H
A-202.		-NH-CH_2-	-CH_2-	-CH_2CH_3, H
A-203.		-NH-CH_2-	-CH_2-	-CH_2CH_3, H
A-204.		-NH-CH_2-	-CH_2-	-CH_2CH_3, H

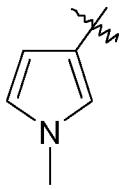
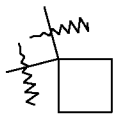
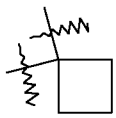
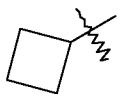
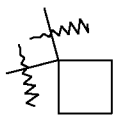
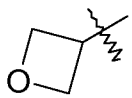
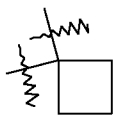
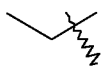
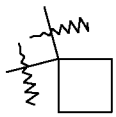
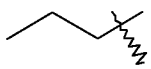
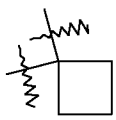
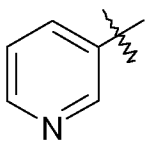
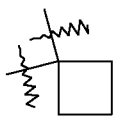
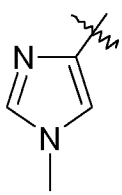
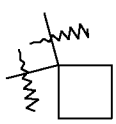
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-205.		-NH-CH_2-	-CH_2-	-CH_2CH_3, H
A-206.		-NH-CH_2-	-CH_2-	-CH_2CH_3, H
A-207.		-NH-CH_2-	-CH_2-	-CH_2CH_3, H
A-208.		-NH-$(CH_2)_3$-	-CH_2-	-CH_2CH_3, H
A-209.		-NH-$(CH_2)_3$-	-CH_2-	-CH_2CH_3, H
A-210.		-NH-$(CH_2)_3$-	-CH_2-	-CH_2CH_3, H
A-211.		-NH-$(CH_2)_3$-	-CH_2-	-CH_2CH_3, H
A-212.		-NH-$(CH_2)_3$-	-CH_2-	-CH_2CH_3, H

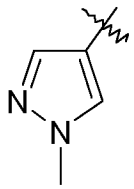
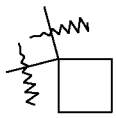
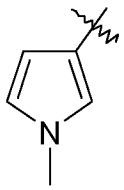
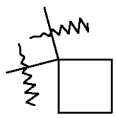
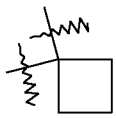
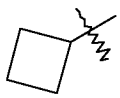
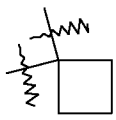
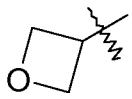
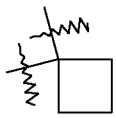
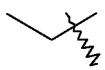
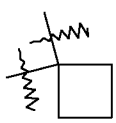
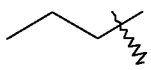
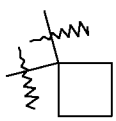
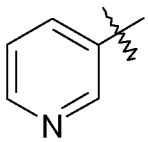
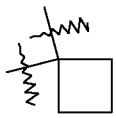
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-213.		-NH-$(CH_2)_3$-	-CH_2-	-CH_2CH_3, H
A-214.		-NH-$(CH_2)_3$-	-CH_2-	-CH_2CH_3, H
A-215.		-NH-$(CH_2)_3$-	-CH_2-	-CH_2CH_3, H
A-216.		-NH-$(CH_2)_3$-	-CH_2-	-CH_2CH_3, H
A-217.		-$(CH_2)_2$-	-CH_2-	-CH_2CH_3, H
A-218.		-$(CH_2)_2$-	-CH_2-	-CH_2CH_3, H
A-219.		-$(CH_2)_2$-	-CH_2-	-CH_2CH_3, H
A-220.		-$(CH_2)_2$-	-CH_2-	-CH_2CH_3, H

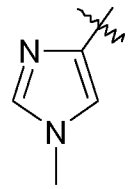
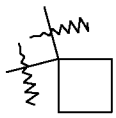
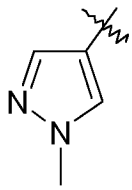
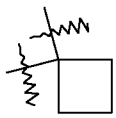
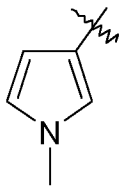
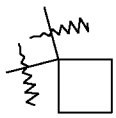
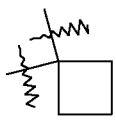
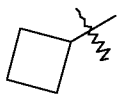
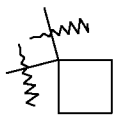
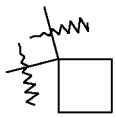
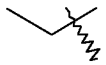
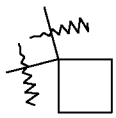
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-221.		-$(CH_2)_2$-	-CH_2-	-CH_2CH_3, H
A-222.		-$(CH_2)_2$-	-CH_2-	-CH_2CH_3, H
A-223.		-$(CH_2)_2$-	-CH_2-	-CH_2CH_3, H
A-224.		-$(CH_2)_2$-	-CH_2-	-CH_2CH_3, H
A-225.		-$(CH_2)_2$-	-CH_2-	-CH_2CH_3, H
A-226.		-NH-$(CH_2)_2$-O-		-CH_2CH_3, H
A-227.		-NH-$(CH_2)_2$-O-		-CH_2CH_3, H
A-228.		-NH-$(CH_2)_2$-O-		-CH_2CH_3, H

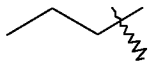
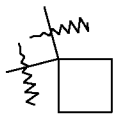
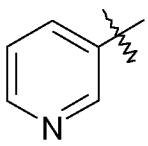
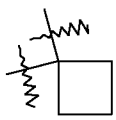
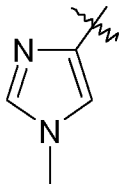
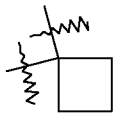
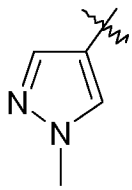
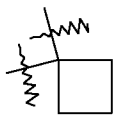
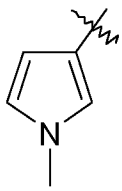
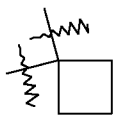
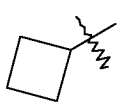
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-229.		$-NH-(CH_2)_2-O-$		$-CH_2CH_3$, H
A-230.		$-NH-(CH_2)_2-O-$		$-CH_2CH_3$, H
A-231.		$-NH-(CH_2)_2-O-$		$-CH_2CH_3$, H
A-232.		$-NH-(CH_2)_2-O-$		$-CH_2CH_3$, H
A-233.		$-NH-(CH_2)_2-O-$		$-CH_2CH_3$, H
A-234.		$-NH-(CH_2)_2-O-$		$-CH_2CH_3$, H
A-235.		$-NH-(CH_2)_2-$		$-CH_2CH_3$, H

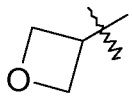
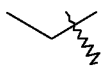
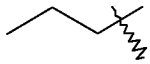
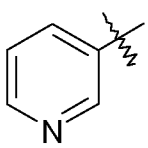
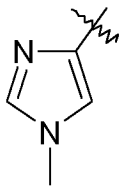
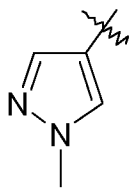
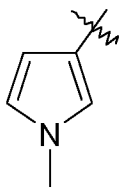
	R^1	-Y-A^2-X^1-	$>CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-236.		-NH-$(CH_2)_2$-		-CH_2CH_3, H
A-237.		-NH-$(CH_2)_2$-		-CH_2CH_3, H
A-238.		-NH-$(CH_2)_2$-		-CH_2CH_3, H
A-239.		-NH-$(CH_2)_2$-		-CH_2CH_3, H
A-240.		-NH-$(CH_2)_2$-		-CH_2CH_3, H
A-241.		-NH-$(CH_2)_2$-		-CH_2CH_3, H
A-242.		-NH-$(CH_2)_2$-		-CH_2CH_3, H

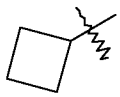
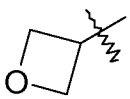
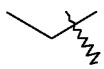
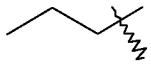
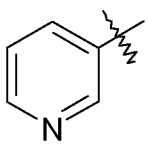
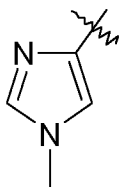
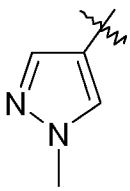
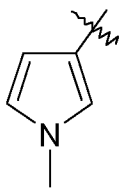
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-243.		-NH-$(CH_2)_2$-		-CH_2CH_3, H
A-244.		-NH-CH_2-		-CH_2CH_3, H
A-245.		-NH-CH_2-		-CH_2CH_3, H
A-246.		-NH-CH_2-		-CH_2CH_3, H
A-247.		-NH-CH_2-		-CH_2CH_3, H
A-248.		-NH-CH_2-		-CH_2CH_3, H
A-249.		-NH-CH_2-		-CH_2CH_3, H
A-250.		-NH-CH_2-		-CH_2CH_3, H

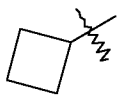
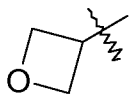
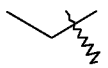
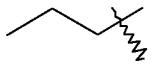
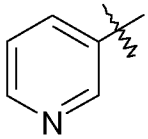
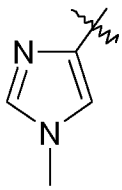
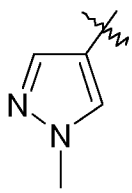
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-251.		-NH-CH_2-		-CH_2CH_3, H
A-252.		-NH-CH_2-		-CH_2CH_3, H
A-253.		-NH-$(CH_2)_3$-		-CH_2CH_3, H
A-254.		-NH-$(CH_2)_3$-		-CH_2CH_3, H
A-255.		-NH-$(CH_2)_3$-		-CH_2CH_3, H
A-256.		-NH-$(CH_2)_3$-		-CH_2CH_3, H
A-257.		-NH-$(CH_2)_3$-		-CH_2CH_3, H
A-258.		-NH-$(CH_2)_3$-		-CH_2CH_3, H

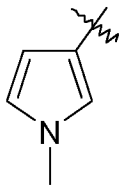
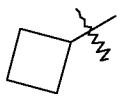
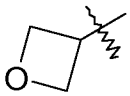
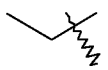
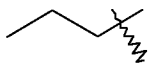
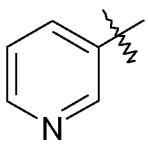
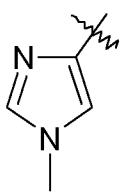
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-259.		$-NH-(CH_2)_3-$		$-CH_2CH_3$, H
A-260.		$-NH-(CH_2)_3-$		$-CH_2CH_3$, H
A-261.		$-NH-(CH_2)_3-$		$-CH_2CH_3$, H
A-262.		$-(CH_2)_2-$		$-CH_2CH_3$, H
A-263.		$-(CH_2)_2-$		$-CH_2CH_3$, H
A-264.		$-(CH_2)_2-$		$-CH_2CH_3$, H
A-265.		$-(CH_2)_2-$		$-CH_2CH_3$, H

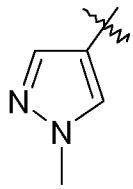
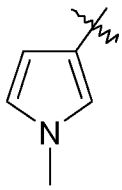
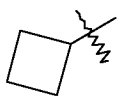
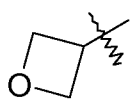
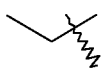
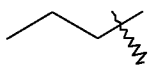
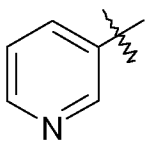
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-266.		$-(CH_2)_2-$		$-CH_2CH_3$, H
A-267.		$-(CH_2)_2-$		$-CH_2CH_3$, H
A-268.		$-(CH_2)_2-$		$-CH_2CH_3$, H
A-269.		$-(CH_2)_2-$		$-CH_2CH_3$, H
A-270.		$-(CH_2)_2-$		$-CH_2CH_3$, H
A-271.		$-NH-(CH_2)_2-O-$	$-CH_2-$	$-(CH_2)_3-$
A-272.		$-NH-(CH_2)_2-O-$	$-CH_2-$	$-(CH_2)_3-$

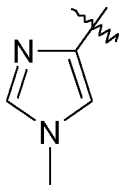
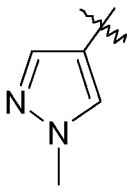
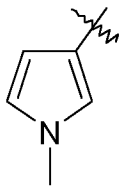
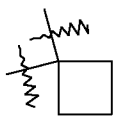
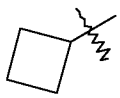
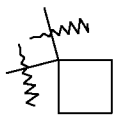
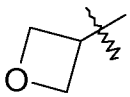
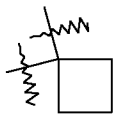
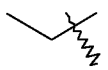
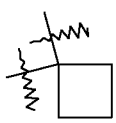
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-273.		-NH-$(CH_2)_2$-O-	-CH_2-	-$(CH_2)_3$-
A-274.		-NH-$(CH_2)_2$-O-	-CH_2-	-$(CH_2)_3$-
A-275.		-NH-$(CH_2)_2$-O-	-CH_2-	-$(CH_2)_3$-
A-276.		-NH-$(CH_2)_2$-O-	-CH_2-	-$(CH_2)_3$-
A-277.		-NH-$(CH_2)_2$-O-	-CH_2-	-$(CH_2)_3$-
A-278.		-NH-$(CH_2)_2$-O-	-CH_2-	-$(CH_2)_3$-
A-279.		-NH-$(CH_2)_2$-O-	-CH_2-	-$(CH_2)_3$-
A-280.		-NH-$(CH_2)_2$-	-CH_2-	-$(CH_2)_3$-

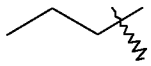
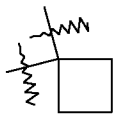
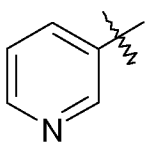
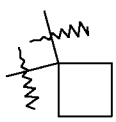
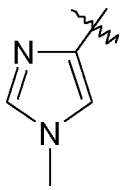
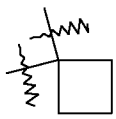
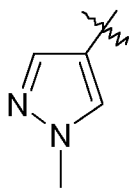
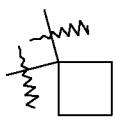
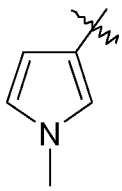
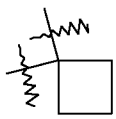
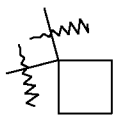
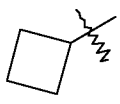
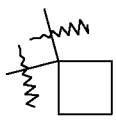
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-281.		-NH-$(CH_2)_2$-	-CH_2-	-$(CH_2)_3$-
A-282.		-NH-$(CH_2)_2$-	-CH_2-	-$(CH_2)_3$-
A-283.		-NH-$(CH_2)_2$-	-CH_2-	-$(CH_2)_3$-
A-284.		-NH-$(CH_2)_2$-	-CH_2-	-$(CH_2)_3$-
A-285.		-NH-$(CH_2)_2$-	-CH_2-	-$(CH_2)_3$-
A-286.		-NH-$(CH_2)_2$-	-CH_2-	-$(CH_2)_3$-
A-287.		-NH-$(CH_2)_2$-	-CH_2-	-$(CH_2)_3$-
A-288.		-NH-$(CH_2)_2$-	-CH_2-	-$(CH_2)_3$-

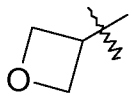
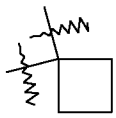
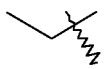
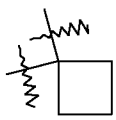
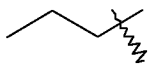
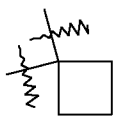
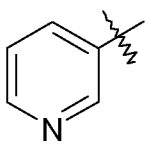
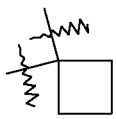
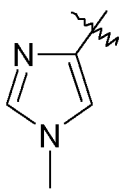
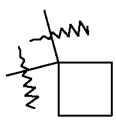
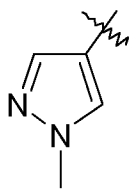
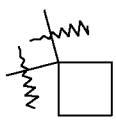
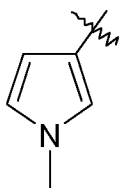
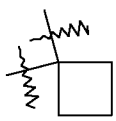
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-289.		-NH-CH_2-	-CH_2-	-$(CH_2)_3$-
A-290.		-NH-CH_2-	-CH_2-	-$(CH_2)_3$-
A-291.		-NH-CH_2-	-CH_2-	-$(CH_2)_3$-
A-292.		-NH-CH_2-	-CH_2-	-$(CH_2)_3$-
A-293.		-NH-CH_2-	-CH_2-	-$(CH_2)_3$-
A-294.		-NH-CH_2-	-CH_2-	-$(CH_2)_3$-
A-295.		-NH-CH_2-	-CH_2-	-$(CH_2)_3$-
A-296.		-NH-CH_2-	-CH_2-	-$(CH_2)_3$-

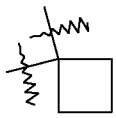
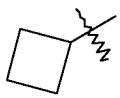
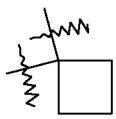
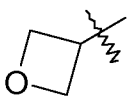
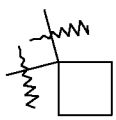
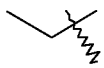
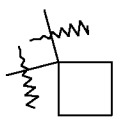
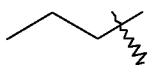
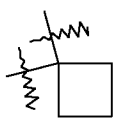
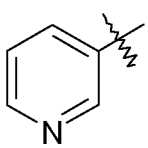
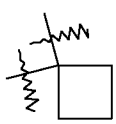
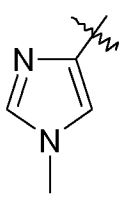
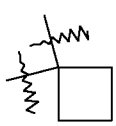
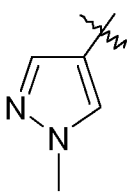
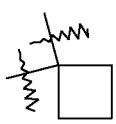
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-297.		-NH-CH_2-	-CH_2-	-$(CH_2)_3$-
A-298.		-NH-$(CH_2)_3$-	-CH_2-	-$(CH_2)_3$-
A-299.		-NH-$(CH_2)_3$-	-CH_2-	-$(CH_2)_3$-
A-300.		-NH-$(CH_2)_3$-	-CH_2-	-$(CH_2)_3$-
A-301.		-NH-$(CH_2)_3$-	-CH_2-	-$(CH_2)_3$-
A-302.		-NH-$(CH_2)_3$-	-CH_2-	-$(CH_2)_3$-
A-303.		-NH-$(CH_2)_3$-	-CH_2-	-$(CH_2)_3$-
A-304.		-NH-$(CH_2)_3$-	-CH_2-	-$(CH_2)_3$-

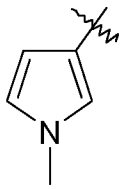
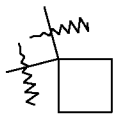
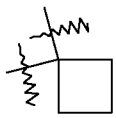
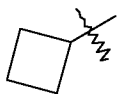
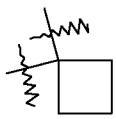
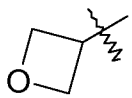
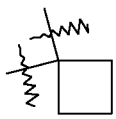
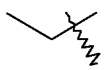
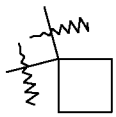
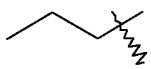
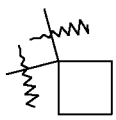
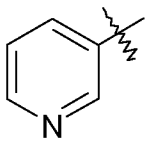
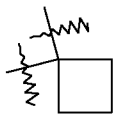
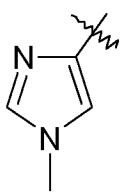
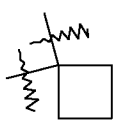
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-305.		-NH-$(CH_2)_3$-	-CH_2-	-$(CH_2)_3$-
A-306.		-NH-$(CH_2)_3$-	-CH_2-	-$(CH_2)_3$-
A-307.		-$(CH_2)_2$-	-CH_2-	-$(CH_2)_3$-
A-308.		-$(CH_2)_2$-	-CH_2-	-$(CH_2)_3$-
A-309.		-$(CH_2)_2$-	-CH_2-	-$(CH_2)_3$-
A-310.		-$(CH_2)_2$-	-CH_2-	-$(CH_2)_3$-
A-311.		-$(CH_2)_2$-	-CH_2-	-$(CH_2)_3$-
A-312.		-$(CH_2)_2$-	-CH_2-	-$(CH_2)_3$-

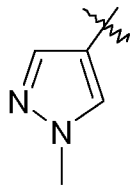
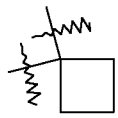
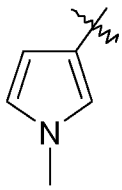
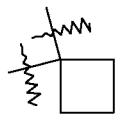
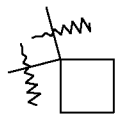
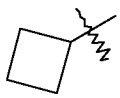
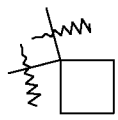
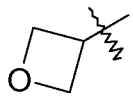
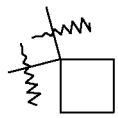
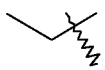
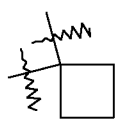
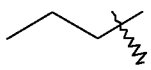
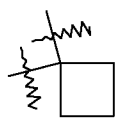
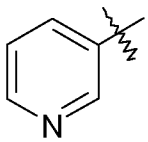
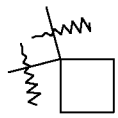
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-313.		-$(CH_2)_2$-	-CH_2-	-$(CH_2)_3$-
A-314.		-$(CH_2)_2$-	-CH_2-	-$(CH_2)_3$-
A-315.		-$(CH_2)_2$-	-CH_2-	-$(CH_2)_3$-
A-316.		-NH-$(CH_2)_2$-O-		-$(CH_2)_3$-
A-317.		-NH-$(CH_2)_2$-O-		-$(CH_2)_3$-
A-318.		-NH-$(CH_2)_2$-O-		-$(CH_2)_3$-
A-319.		-NH-$(CH_2)_2$-O-		-$(CH_2)_3$-

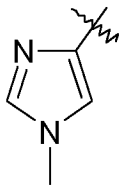
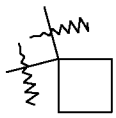
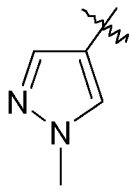
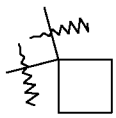
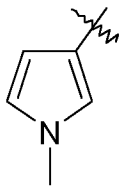
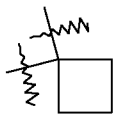
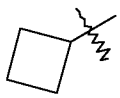
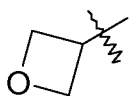
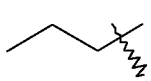
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-320.		-NH-$(CH_2)_2$-O-		-$(CH_2)_3$-
A-321.		-NH-$(CH_2)_2$-O-		-$(CH_2)_3$-
A-322.		-NH-$(CH_2)_2$-O-		-$(CH_2)_3$-
A-323.		-NH-$(CH_2)_2$-O-		-$(CH_2)_3$-
A-324.		-NH-$(CH_2)_2$-O-		-$(CH_2)_3$-
A-325.		-NH-$(CH_2)_2$-		-$(CH_2)_3$-
A-326.		-NH-$(CH_2)_2$-		-$(CH_2)_3$-

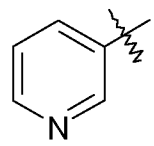
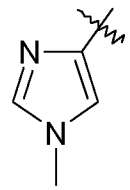
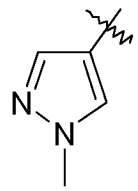
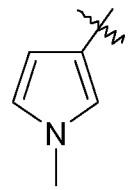
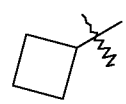
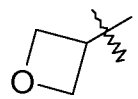
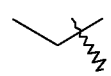
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-327.		$-NH-(CH_2)_2-$		$-(CH_2)_3-$
A-328.		$-NH-(CH_2)_2-$		$-(CH_2)_3-$
A-329.		$-NH-(CH_2)_2-$		$-(CH_2)_3-$
A-330.		$-NH-(CH_2)_2-$		$-(CH_2)_3-$
A-331.		$-NH-(CH_2)_2-$		$-(CH_2)_3-$
A-332.		$-NH-(CH_2)_2-$		$-(CH_2)_3-$
A-333.		$-NH-(CH_2)_2-$		$-(CH_2)_3-$

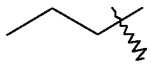
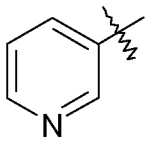
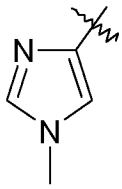
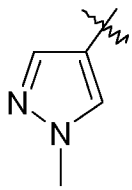
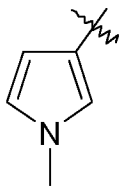
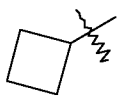
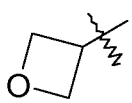
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-334.		-NH-CH_2-		-$(CH_2)_3$-
A-335.		-NH-CH_2-		-$(CH_2)_3$-
A-336.		-NH-CH_2-		-$(CH_2)_3$-
A-337.		-NH-CH_2-		-$(CH_2)_3$-
A-338.		-NH-CH_2-		-$(CH_2)_3$-
A-339.		-NH-CH_2-		-$(CH_2)_3$-
A-340.		-NH-CH_2-		-$(CH_2)_3$-
A-341.		-NH-CH_2-		-$(CH_2)_3$-

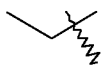
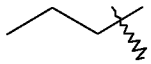
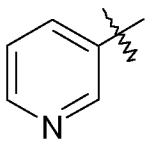
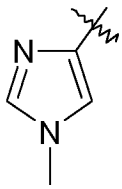
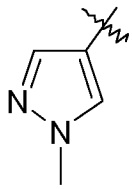
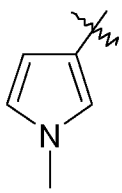
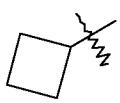
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-342.		-NH-CH_2-		-$(CH_2)_3$-
A-343.		-NH-$(CH_2)_3$-		-$(CH_2)_3$-
A-344.		-NH-$(CH_2)_3$-		-$(CH_2)_3$-
A-345.		-NH-$(CH_2)_3$-		-$(CH_2)_3$-
A-346.		-NH-$(CH_2)_3$-		-$(CH_2)_3$-
A-347.		-NH-$(CH_2)_3$-		-$(CH_2)_3$-
A-348.		-NH-$(CH_2)_3$-		-$(CH_2)_3$-
A-349.		-NH-$(CH_2)_3$-		-$(CH_2)_3$-

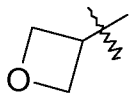
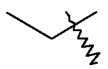
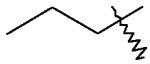
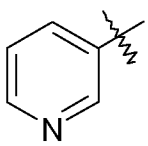
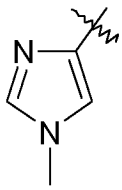
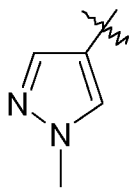
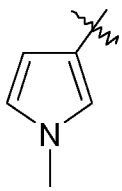
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-350.		-NH-$(CH_2)_3$-		-$(CH_2)_3$-
A-351.		-NH-$(CH_2)_3$-		-$(CH_2)_3$-
A-352.		-$(CH_2)_2$-		-$(CH_2)_3$-
A-353.		-$(CH_2)_2$-		-$(CH_2)_3$-
A-354.		-$(CH_2)_2$-		-$(CH_2)_3$-
A-355.		-$(CH_2)_2$-		-$(CH_2)_3$-
A-356.		-$(CH_2)_2$-		-$(CH_2)_3$-
A-357.		-$(CH_2)_2$-		-$(CH_2)_3$-

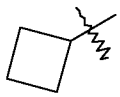
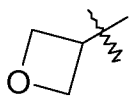
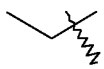
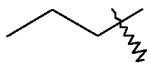
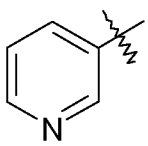
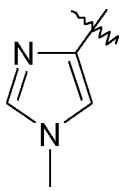
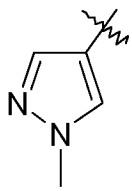
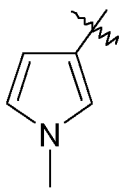
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-358.		$-(CH_2)_2-$		$-(CH_2)_3-$
A-359.		$-(CH_2)_2-$		$-(CH_2)_3-$
A-360.		$-(CH_2)_2-$		$-(CH_2)_3-$
A-361.		$-NH-(CH_2)_2-O-$	$-CH_2-$	$-(CH_2)_4-$
A-362.		$-NH-(CH_2)_2-O-$	$-CH_2-$	$-(CH_2)_4-$
A-363.		$-NH-(CH_2)_2-O-$	$-CH_2-$	$-(CH_2)_4-$
A-364.		$-NH-(CH_2)_2-O-$	$-CH_2-$	$-(CH_2)_4-$
A-365.		$-NH-(CH_2)_2-O-$	$-CH_2-$	$-(CH_2)_4-$

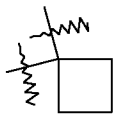
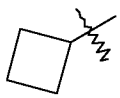
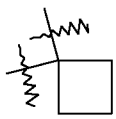
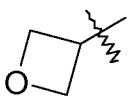
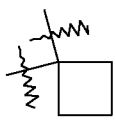
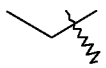
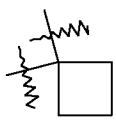
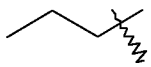
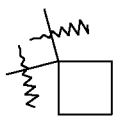
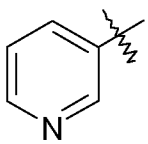
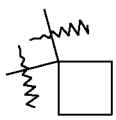
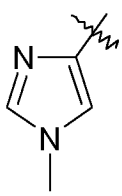
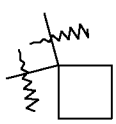
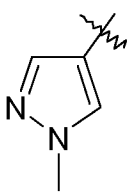
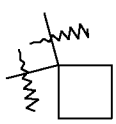
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-366.		-NH-$(CH_2)_2$-O-	-CH_2-	-$(CH_2)_4$-
A-367.		-NH-$(CH_2)_2$-O-	-CH_2-	-$(CH_2)_4$-
A-368.		-NH-$(CH_2)_2$-O-	-CH_2-	-$(CH_2)_4$-
A-369.		-NH-$(CH_2)_2$-O-	-CH_2-	-$(CH_2)_4$-
A-370.		-NH-$(CH_2)_2$-	-CH_2-	-$(CH_2)_4$-
A-371.		-NH-$(CH_2)_2$-	-CH_2-	-$(CH_2)_4$-
A-372.		-NH-$(CH_2)_2$-	-CH_2-	-$(CH_2)_4$-
A-373.		-NH-$(CH_2)_2$-	-CH_2-	-$(CH_2)_4$-

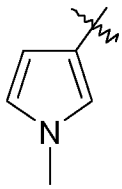
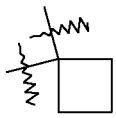
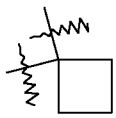
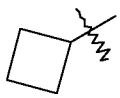
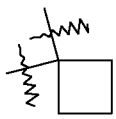
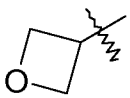
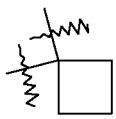
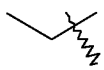
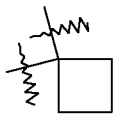
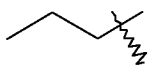
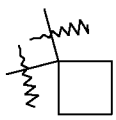
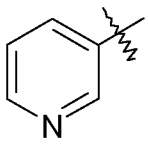
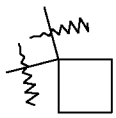
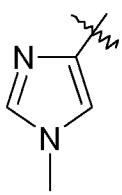
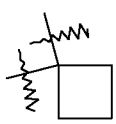
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-374.		-NH-$(CH_2)_2$-	-CH_2-	-$(CH_2)_4$-
A-375.		-NH-$(CH_2)_2$-	-CH_2-	-$(CH_2)_4$-
A-376.		-NH-$(CH_2)_2$-	-CH_2-	-$(CH_2)_4$-
A-377.		-NH-$(CH_2)_2$-	-CH_2-	-$(CH_2)_4$-
A-378.		-NH-$(CH_2)_2$-	-CH_2-	-$(CH_2)_4$-
A-379.		-NH-CH_2-	-CH_2-	-$(CH_2)_4$-
A-380.		-NH-CH_2-	-CH_2-	-$(CH_2)_4$-
A-381.		-NH-CH_2-	-CH_2-	-$(CH_2)_4$-

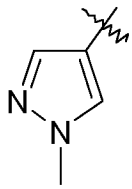
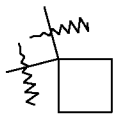
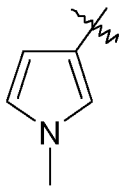
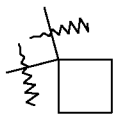
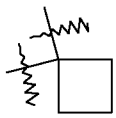
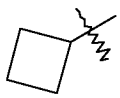
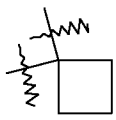
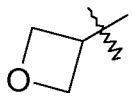
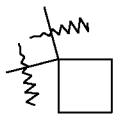
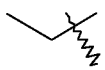
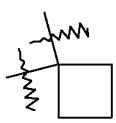
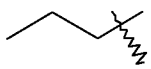
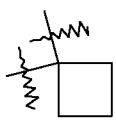
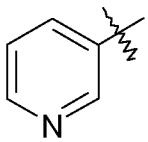
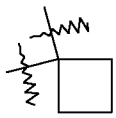
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-382.		-NH-CH_2-	-CH_2-	-$(CH_2)_4$-
A-383.		-NH-CH_2-	-CH_2-	-$(CH_2)_4$-
A-384.		-NH-CH_2-	-CH_2-	-$(CH_2)_4$-
A-385.		-NH-CH_2-	-CH_2-	-$(CH_2)_4$-
A-386.		-NH-CH_2-	-CH_2-	-$(CH_2)_4$-
A-387.		-NH-CH_2-	-CH_2-	-$(CH_2)_4$-
A-388.		-NH-$(CH_2)_3$-	-CH_2-	-$(CH_2)_4$-
A-389.		-NH-$(CH_2)_3$-	-CH_2-	-$(CH_2)_4$-

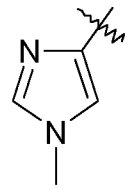
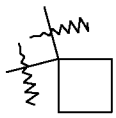
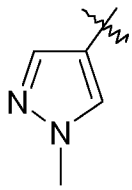
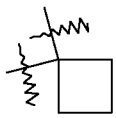
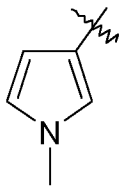
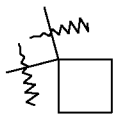
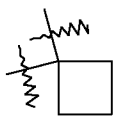
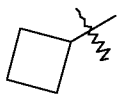
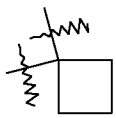
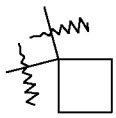
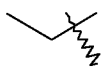
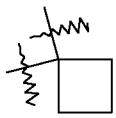
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-390.		-NH-$(CH_2)_3$-	-CH_2-	-$(CH_2)_4$-
A-391.		-NH-$(CH_2)_3$-	-CH_2-	-$(CH_2)_4$-
A-392.		-NH-$(CH_2)_3$-	-CH_2-	-$(CH_2)_4$-
A-393.		-NH-$(CH_2)_3$-	-CH_2-	-$(CH_2)_4$-
A-394.		-NH-$(CH_2)_3$-	-CH_2-	-$(CH_2)_4$-
A-395.		-NH-$(CH_2)_3$-	-CH_2-	-$(CH_2)_4$-
A-396.		-NH-$(CH_2)_3$-	-CH_2-	-$(CH_2)_4$-
A-397.		-$(CH_2)_2$-	-CH_2-	-$(CH_2)_4$-

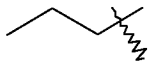
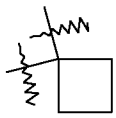
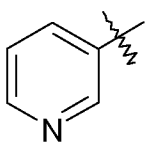
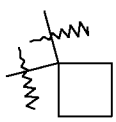
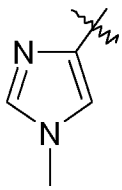
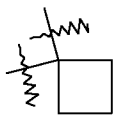
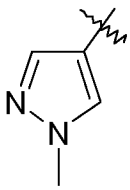
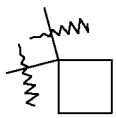
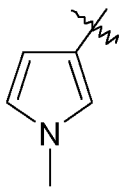
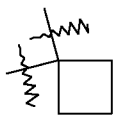
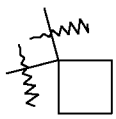
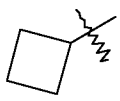
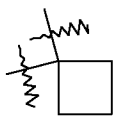
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-398.		-$(CH_2)_2$-	-CH_2-	-$(CH_2)_4$-
A-399.		-$(CH_2)_2$-	-CH_2-	-$(CH_2)_4$-
A-400.		-$(CH_2)_2$-	-CH_2-	-$(CH_2)_4$-
A-401.		-$(CH_2)_2$-	-CH_2-	-$(CH_2)_4$-
A-402.		-$(CH_2)_2$-	-CH_2-	-$(CH_2)_4$-
A-403.		-$(CH_2)_2$-	-CH_2-	-$(CH_2)_4$-
A-404.		-$(CH_2)_2$-	-CH_2-	-$(CH_2)_4$-
A-405.		-$(CH_2)_2$-	-CH_2-	-$(CH_2)_4$-

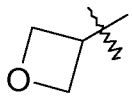
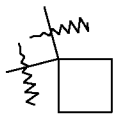
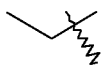
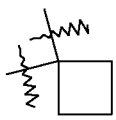
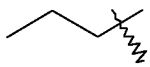
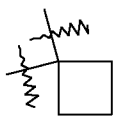
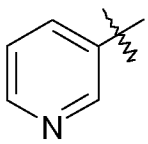
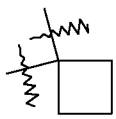
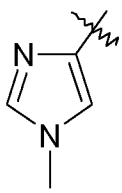
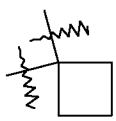
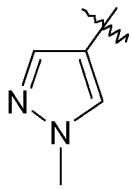
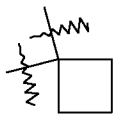
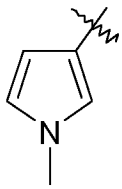
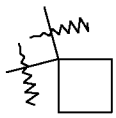
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-406.		$-NH-(CH_2)_2-O-$		$-(CH_2)_4-$
A-407.		$-NH-(CH_2)_2-O-$		$-(CH_2)_4-$
A-408.		$-NH-(CH_2)_2-O-$		$-(CH_2)_4-$
A-409.		$-NH-(CH_2)_2-O-$		$-(CH_2)_4-$
A-410.		$-NH-(CH_2)_2-O-$		$-(CH_2)_4-$
A-411.		$-NH-(CH_2)_2-O-$		$-(CH_2)_4-$
A-412.		$-NH-(CH_2)_2-O-$		$-(CH_2)_4-$
A-413.		$-NH-(CH_2)_2-O-$		$-(CH_2)_4-$

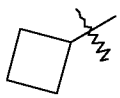
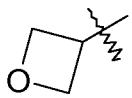
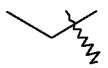
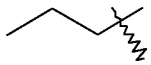
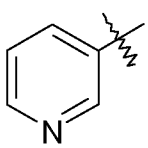
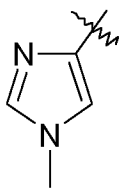
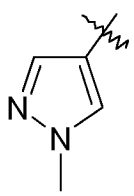
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-414.		-NH-$(CH_2)_2$-O-		-$(CH_2)_4$-
A-415.		-NH-$(CH_2)_2$-		-$(CH_2)_4$-
A-416.		-NH-$(CH_2)_2$-		-$(CH_2)_4$-
A-417.		-NH-$(CH_2)_2$-		-$(CH_2)_4$-
A-418.		-NH-$(CH_2)_2$-		-$(CH_2)_4$-
A-419.		-NH-$(CH_2)_2$-		-$(CH_2)_4$-
A-420.		-NH-$(CH_2)_2$-		-$(CH_2)_4$-
A-421.		-NH-$(CH_2)_2$-		-$(CH_2)_4$-

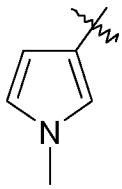
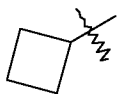
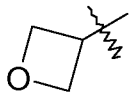
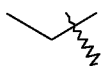
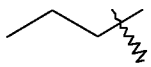
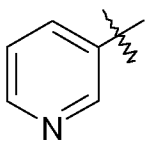
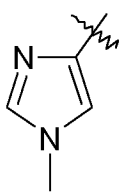
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-422.		$-NH-(CH_2)_2-$		$-(CH_2)_4-$
A-423.		$-NH-(CH_2)_2-$		$-(CH_2)_4-$
A-424.		$-NH-CH_2-$		$-(CH_2)_4-$
A-425.		$-NH-CH_2-$		$-(CH_2)_4-$
A-426.		$-NH-CH_2-$		$-(CH_2)_4-$
A-427.		$-NH-CH_2-$		$-(CH_2)_4-$
A-428.		$-NH-CH_2-$		$-(CH_2)_4-$
A-429.		$-NH-CH_2-$		$-(CH_2)_4-$

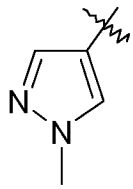
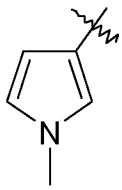
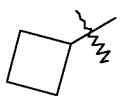
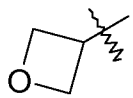
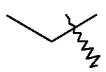
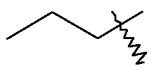
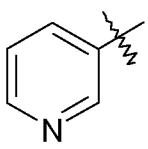
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-430.		$-NH-CH_2-$		$-(CH_2)_4-$
A-431.		$-NH-CH_2-$		$-(CH_2)_4-$
A-432.		$-NH-CH_2-$		$-(CH_2)_4-$
A-433.		$-NH-(CH_2)_3-$		$-(CH_2)_4-$
A-434.		$-NH-(CH_2)_3-$		$-(CH_2)_4-$
A-435.		$-NH-(CH_2)_3-$		$-(CH_2)_4-$
A-436.		$-NH-(CH_2)_3-$		$-(CH_2)_4-$

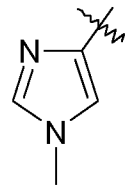
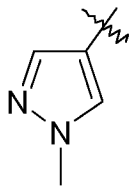
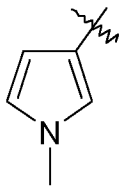
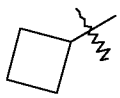
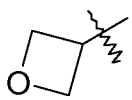
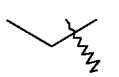
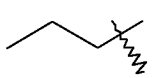
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-437.		-NH-$(CH_2)_3$-		-$(CH_2)_4$-
A-438.		-NH-$(CH_2)_3$-		-$(CH_2)_4$-
A-439.		-NH-$(CH_2)_3$-		-$(CH_2)_4$-
A-440.		-NH-$(CH_2)_3$-		-$(CH_2)_4$-
A-441.		-NH-$(CH_2)_3$-		-$(CH_2)_4$-
A-442.		-$(CH_2)_2$-		-$(CH_2)_4$-
A-443.		-$(CH_2)_2$-		-$(CH_2)_4$-

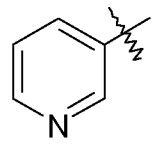
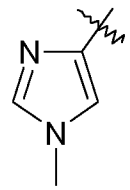
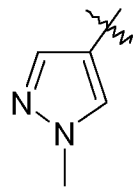
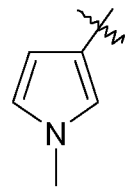
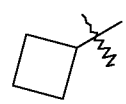
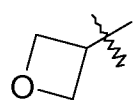
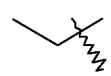
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-444.		$-(CH_2)_2-$		$-(CH_2)_4-$
A-445.		$-(CH_2)_2-$		$-(CH_2)_4-$
A-446.		$-(CH_2)_2-$		$-(CH_2)_4-$
A-447.		$-(CH_2)_2-$		$-(CH_2)_4-$
A-448.		$-(CH_2)_2-$		$-(CH_2)_4-$
A-449.		$-(CH_2)_2-$		$-(CH_2)_4-$
A-450.		$-(CH_2)_2-$		$-(CH_2)_4-$

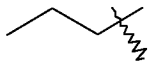
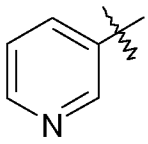
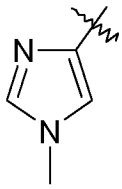
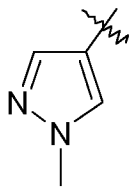
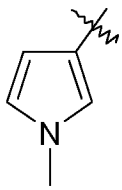
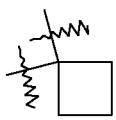
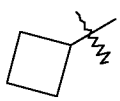
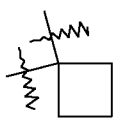
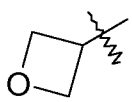
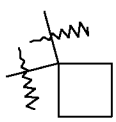
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-451.		-NH-$(CH_2)_2$-O-	-CH_2-	-CH_2 CH_2CH_3, H
A-452.		-NH-$(CH_2)_2$-O-	-CH_2-	-CH_2 CH_2CH_3, H
A-453.		-NH-$(CH_2)_2$-O-	-CH_2-	-CH_2 CH_2CH_3, H
A-454.		-NH-$(CH_2)_2$-O-	-CH_2-	-CH_2 CH_2CH_3, H
A-455.		-NH-$(CH_2)_2$-O-	-CH_2-	-CH_2 CH_2CH_3, H
A-456.		-NH-$(CH_2)_2$-O-	-CH_2-	-CH_2 CH_2CH_3, H
A-457.		-NH-$(CH_2)_2$-O-	-CH_2-	-CH_2 CH_2CH_3, H
A-458.		-NH-$(CH_2)_2$-O-	-CH_2-	-CH_2 CH_2CH_3, H

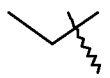
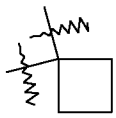
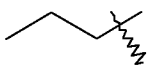
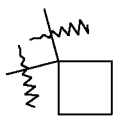
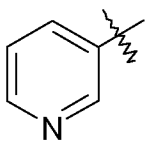
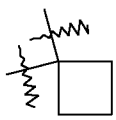
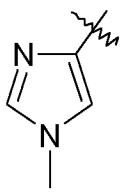
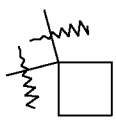
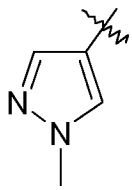
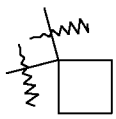
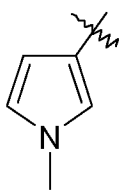
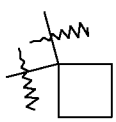
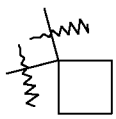
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-459.		-NH-$(CH_2)_2$-O-	-CH_2-	-CH_2 CH_2CH_3, H
A-460.		-NH-$(CH_2)_2$-	-CH_2-	-CH_2 CH_2CH_3, H
A-461.		-NH-$(CH_2)_2$-	-CH_2-	-CH_2 CH_2CH_3, H
A-462.		-NH-$(CH_2)_2$-	-CH_2-	-CH_2 CH_2CH_3, H
A-463.		-NH-$(CH_2)_2$-	-CH_2-	-CH_2 CH_2CH_3, H
A-464.		-NH-$(CH_2)_2$-	-CH_2-	-CH_2 CH_2CH_3, H
A-465.		-NH-$(CH_2)_2$-	-CH_2-	-CH_2 CH_2CH_3, H
A-466.		-NH-$(CH_2)_2$-	-CH_2-	-CH_2 CH_2CH_3, H

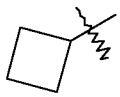
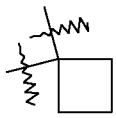
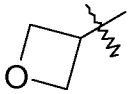
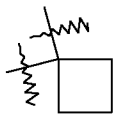
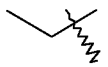
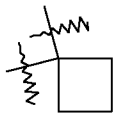
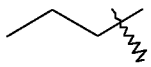
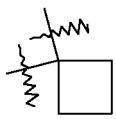
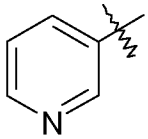
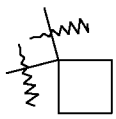
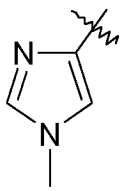
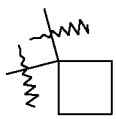
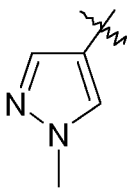
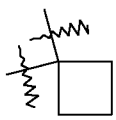
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-467.		-NH-$(CH_2)_2$-	-CH_2-	-CH_2 CH_2CH_3, H
A-468.		-NH-$(CH_2)_2$-	-CH_2-	-CH_2 CH_2CH_3, H
A-469.		-NH-CH_2-	-CH_2-	-CH_2 CH_2CH_3, H
A-470.		-NH-CH_2-	-CH_2-	-CH_2 CH_2CH_3, H
A-471.		-NH-CH_2-	-CH_2-	-CH_2 CH_2CH_3, H
A-472.		-NH-CH_2-	-CH_2-	-CH_2 CH_2CH_3, H
A-473.		-NH-CH_2-	-CH_2-	-CH_2 CH_2CH_3, H
A-474.		-NH-CH_2-	-CH_2-	-CH_2 CH_2CH_3, H

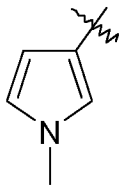
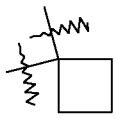
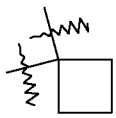
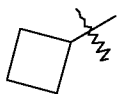
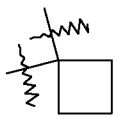
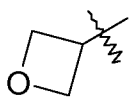
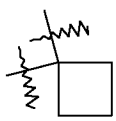
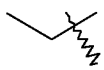
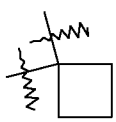
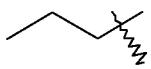
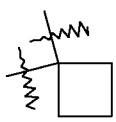
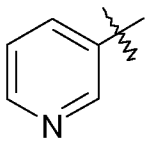
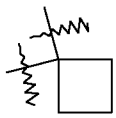
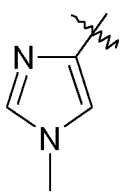
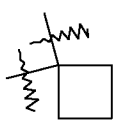
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-475.		$-NH-CH_2-$	$-CH_2-$	$-CH_2$ CH_2CH_3, H
A-476.		$-NH-CH_2-$	$-CH_2-$	$-CH_2$ CH_2CH_3, H
A-477.		$-NH-CH_2-$	$-CH_2-$	$-CH_2$ CH_2CH_3, H
A-478.		$-NH-(CH_2)_3-$	$-CH_2-$	$-CH_2$ CH_2CH_3, H
A-479.		$-NH-(CH_2)_3-$	$-CH_2-$	$-CH_2$ CH_2CH_3, H
A-480.		$-NH-(CH_2)_3-$	$-CH_2-$	$-CH_2$ CH_2CH_3, H
A-481.		$-NH-(CH_2)_3-$	$-CH_2-$	$-CH_2$ CH_2CH_3, H
A-482.		$-NH-(CH_2)_3-$	$-CH_2-$	$-CH_2$ CH_2CH_3, H

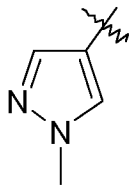
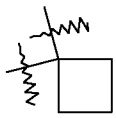
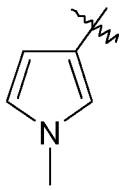
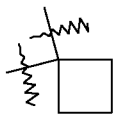
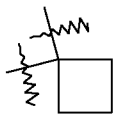
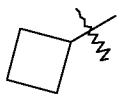
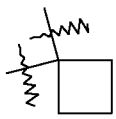
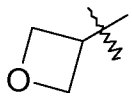
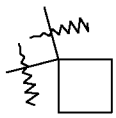
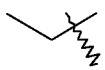
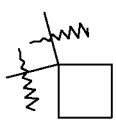
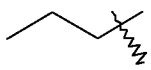
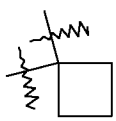
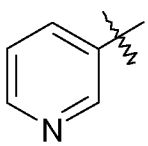
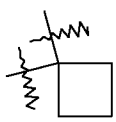
	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-483.		-NH-$(CH_2)_3$-	-CH_2-	-CH_2 CH_2CH_3, H
A-484.		-NH-$(CH_2)_3$-	-CH_2-	-CH_2 CH_2CH_3, H
A-485.		-NH-$(CH_2)_3$-	-CH_2-	-CH_2 CH_2CH_3, H
A-486.		-NH-$(CH_2)_3$-	-CH_2-	-CH_2 CH_2CH_3, H
A-487.		-$(CH_2)_2$-	-CH_2-	-CH_2 CH_2CH_3, H
A-488.		-$(CH_2)_2$-	-CH_2-	-CH_2 CH_2CH_3, H
A-489.		-$(CH_2)_2$-	-CH_2-	-CH_2 CH_2CH_3, H
A-490.		-$(CH_2)_2$-	-CH_2-	-CH_2 CH_2CH_3, H

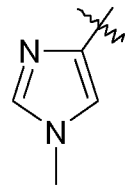
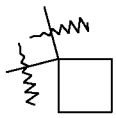
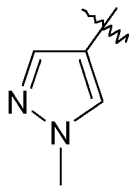
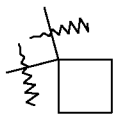
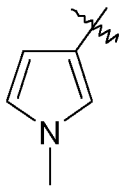
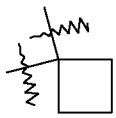
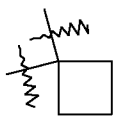
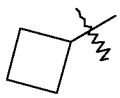
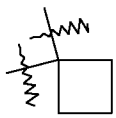
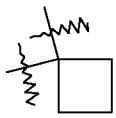
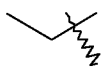
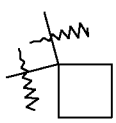
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-491.		$-(CH_2)_2-$	$-CH_2-$	$-CH_2$ CH_2CH_3, H
A-492.		$-(CH_2)_2-$	$-CH_2-$	$-CH_2$ CH_2CH_3, H
A-493.		$-(CH_2)_2-$	$-CH_2-$	$-CH_2$ CH_2CH_3, H
A-494.		$-(CH_2)_2-$	$-CH_2-$	$-CH_2$ CH_2CH_3, H
A-495.		$-(CH_2)_2-$	$-CH_2-$	$-CH_2$ CH_2CH_3, H
A-496.		$-NH-(CH_2)_2-O-$		$-CH_2$ CH_2CH_3, H
A-497.		$-NH-(CH_2)_2-O-$		$-CH_2$ CH_2CH_3, H
A-498.		$-NH-(CH_2)_2-O-$		$-CH_2$ CH_2CH_3, H

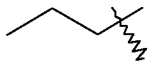
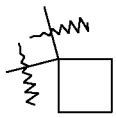
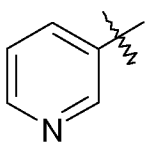
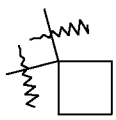
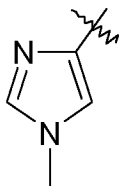
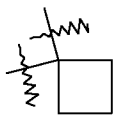
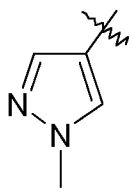
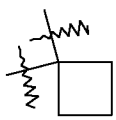
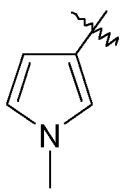
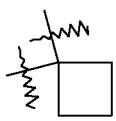
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-499.		$-NH-(CH_2)_2-O-$		$-CH_2$ CH_2CH_3, H
A-500.		$-NH-(CH_2)_2-O-$		$-CH_2$ CH_2CH_3, H
A-501.		$-NH-(CH_2)_2-O-$		$-CH_2$ CH_2CH_3, H
A-502.		$-NH-(CH_2)_2-O-$		$-CH_2$ CH_2CH_3, H
A-503.		$-NH-(CH_2)_2-O-$		$-CH_2$ CH_2CH_3, H
A-504.		$-NH-(CH_2)_2-O-$		$-CH_2$ CH_2CH_3, H
A-505.		$-NH-(CH_2)_2-$		$-CH_2$ CH_2CH_3, H

	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-506.		-NH-$(CH_2)_2$-		-CH_2 CH_2CH_3, H
A-507.		-NH-$(CH_2)_2$-		-CH_2 CH_2CH_3, H
A-508.		-NH-$(CH_2)_2$-		-CH_2 CH_2CH_3, H
A-509.		-NH-$(CH_2)_2$-		-CH_2 CH_2CH_3, H
A-510.		-NH-$(CH_2)_2$-		-CH_2 CH_2CH_3, H
A-511.		-NH-$(CH_2)_2$-		-CH_2 CH_2CH_3, H
A-512.		-NH-$(CH_2)_2$-		-CH_2 CH_2CH_3, H

	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-513.		-NH-$(CH_2)_2$-		-CH_2 CH_2CH_3, H
A-514.		-NH-CH_2-		-CH_2 CH_2CH_3, H
A-515.		-NH-CH_2-		-CH_2 CH_2CH_3, H
A-516.		-NH-CH_2-		-CH_2 CH_2CH_3, H
A-517.		-NH-CH_2-		-CH_2 CH_2CH_3, H
A-518.		-NH-CH_2-		-CH_2 CH_2CH_3, H
A-519.		-NH-CH_2-		-CH_2 CH_2CH_3, H
A-520.		-NH-CH_2-		-CH_2 CH_2CH_3, H

	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-521.		$-NH-CH_2-$		$-CH_2$ CH_2CH_3, H
A-522.		$-NH-CH_2-$		$-CH_2$ CH_2CH_3, H
A-523.		$-NH-(CH_2)_3-$		$-CH_2$ CH_2CH_3, H
A-524.		$-NH-(CH_2)_3-$		$-CH_2$ CH_2CH_3, H
A-525.		$-NH-(CH_2)_3-$		$-CH_2$ CH_2CH_3, H
A-526.		$-NH-(CH_2)_3-$		$-CH_2$ CH_2CH_3, H
A-527.		$-NH-(CH_2)_3-$		$-CH_2$ CH_2CH_3, H
A-528.		$-NH-(CH_2)_3-$		$-CH_2$ CH_2CH_3, H

	R^1	-Y-A^2-X^1-	>$CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-529.		-NH-$(CH_2)_3$-		-CH_2 CH_2CH_3, H
A-530.		-NH-$(CH_2)_3$-		-CH_2 CH_2CH_3, H
A-531.		-NH-$(CH_2)_3$-		-CH_2 CH_2CH_3, H
A-532.		-$(CH_2)_2$-		-CH_2 CH_2CH_3, H
A-533.		-$(CH_2)_2$-		-CH_2 CH_2CH_3, H
A-534.		-$(CH_2)_2$-		-CH_2 CH_2CH_3, H
A-535.		-$(CH_2)_2$-		-CH_2 CH_2CH_3, H

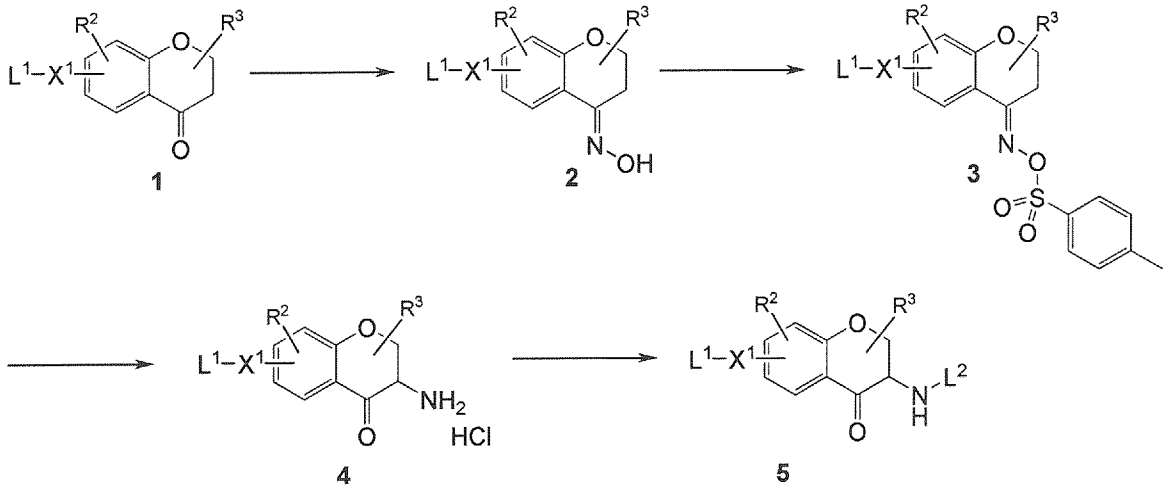
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	R^{4a}, R^{4b}
A-536.		$-(CH_2)_2-$		$-CH_2$ CH_2CH_3, H
A-537.		$-(CH_2)_2-$		$-CH_2$ CH_2CH_3, H
A-538.		$-(CH_2)_2-$		$-CH_2$ CH_2CH_3, H
A-539.		$-(CH_2)_2-$		$-CH_2$ CH_2CH_3, H
A-540.		$-(CH_2)_2-$		$-CH_2$ CH_2CH_3, H

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^1 is -O-.

Scheme 1:

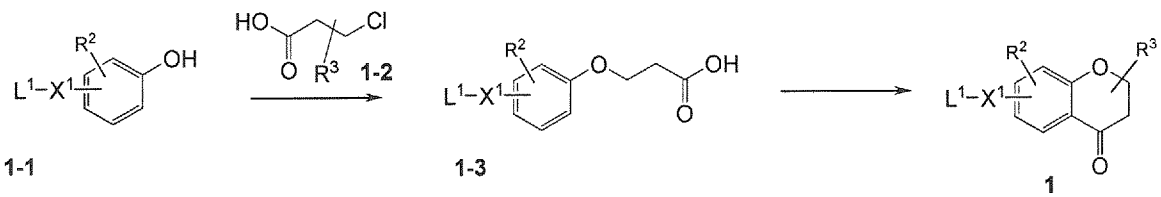


As shown in scheme 1, the compound of general formula 1 can be transferred into the corresponding hydroxylamine 2 (e.g. in presence of NH_2OH HCl). The hydroxyl group can be converted to a leaving group (e.g. tosyl or mesyl) to yield compounds of the general formula 3. Compounds 3 readily undergo Neber rearrangement in the presence of a base (e.g. NaOEt, J. Med. Chem. 1988, *31*, 2178) followed by protection with a suitable protecting group L^2 (e.g. L^2 = COOEt) to give the compound of general formula 5.

In scheme 1, the variables R^2, R^3 are as defined herein and L^1 a suitable protecting group (e.g. L^1 = Me). The process depicted in scheme 1 is also useful for obtaining aminochromanes, wherein X is optionally substituted alkylene. In this case, L^1 is a group that represents, or can be converted into, the desired side chain R^1-W-A^1-Q-Y-A^2-.

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 X^1 is -O- and L^1 is a suitable protecting group (e.g. L^1 = Me).

Scheme 2:

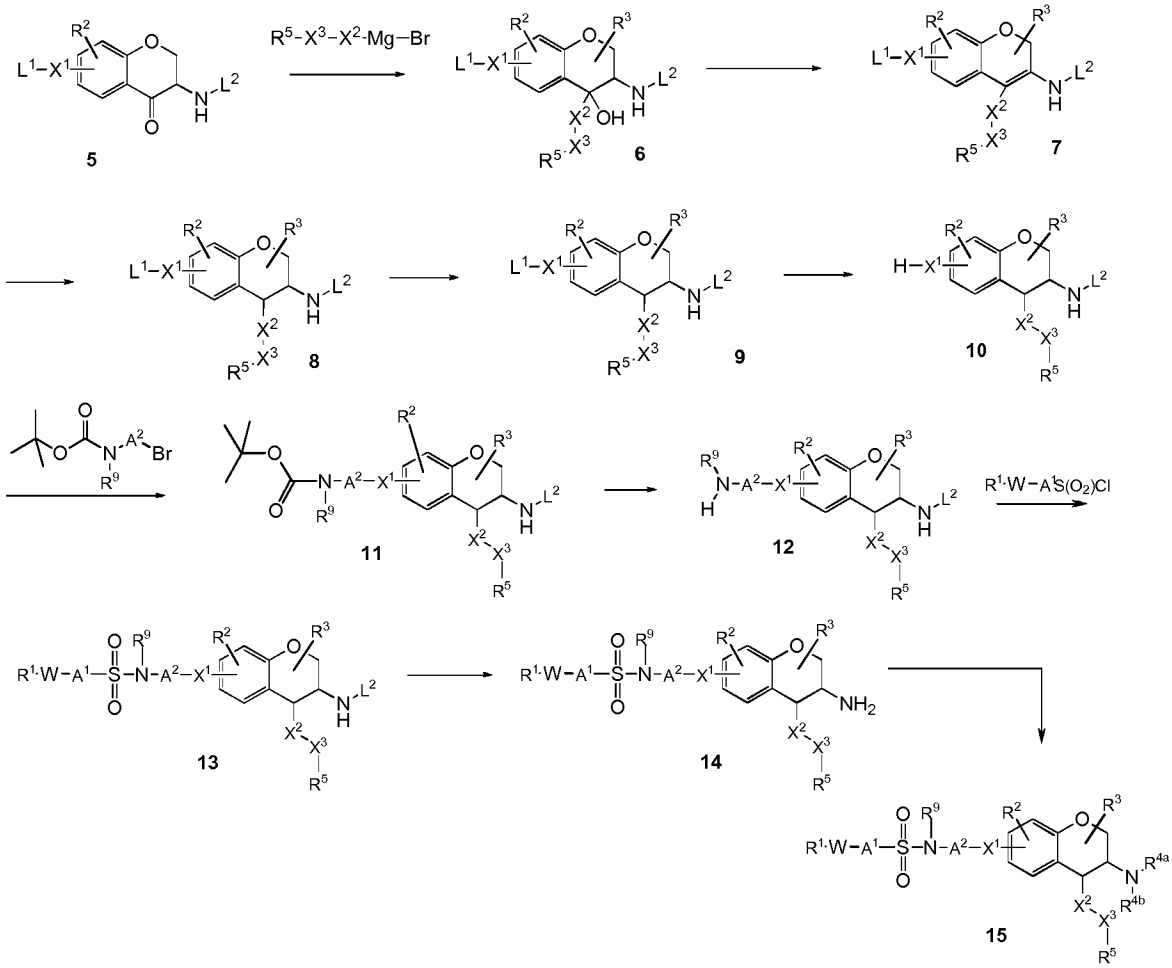


Phenols of the general formula 1-1 can be reacted with 3-halogenated carboxylic acids like 1-2 in presence of a base as described in the literature (e.g. potassium hydroxide, sodium hydrogencarbonate, J. Med. Chem. 1982, *25*, 393) to give compounds of the general formula 1-3. In presence of an acid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

In scheme 2, the variables R^2, R^3 are as defined herein.

The process depicted in scheme 3 is useful for obtaining aminochromanes, wherein X^1 is -O- or -S-, A^2 is optionally substituted alkylene, Y is $-NR^9-$, and Q is $-S(O)_2$.

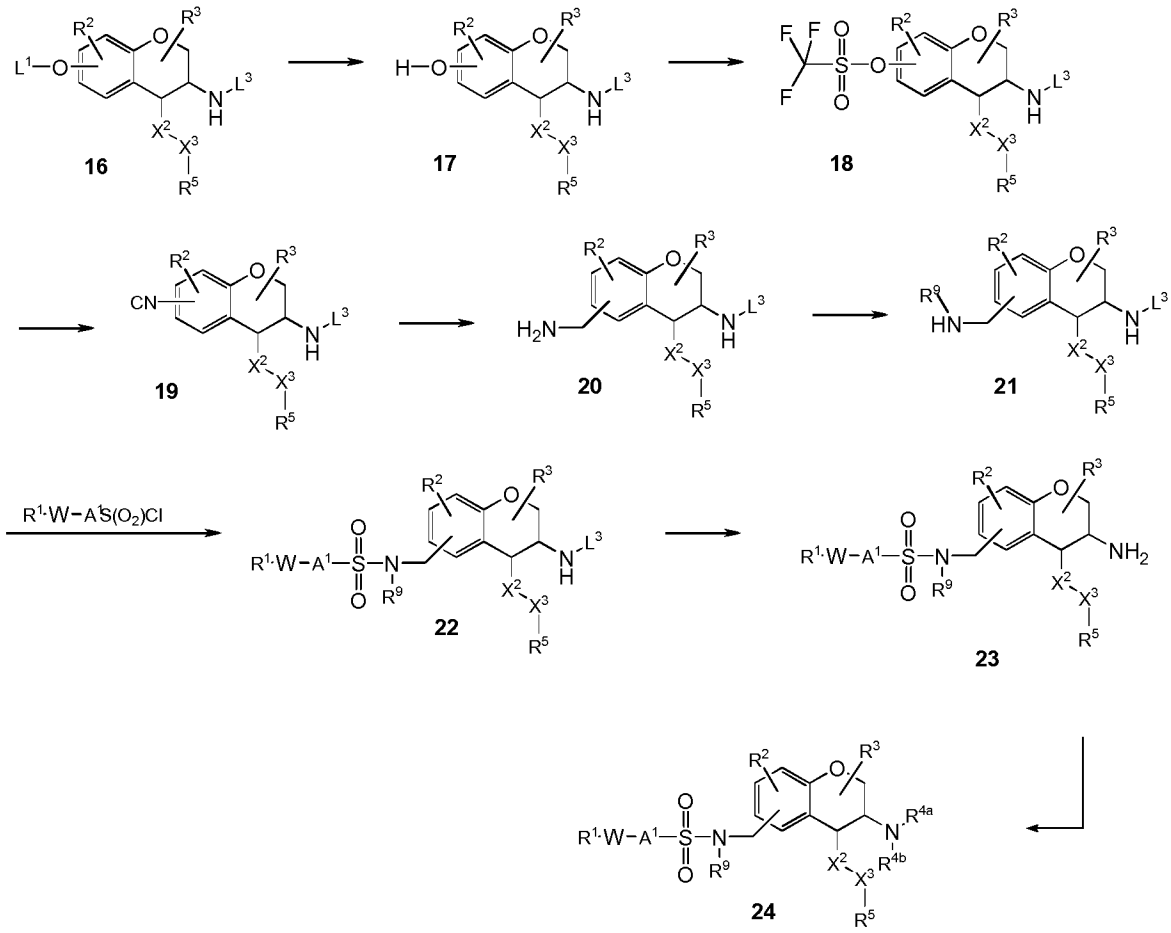
Scheme 3:



In scheme 3, the variables L^1, R^1, W, A^1, R^2, R^3, R^{4a}, R^{4b}, R^5, R^9, X^2, X^3 are as defined herein and L^2 is a suitable protecting group (e.g. L^2 = COOEt).

The process depicted in scheme 4 is useful for obtaining aminochromanes, wherein X^1 is methylene, A^2 is a bond, Y is $-NR^9-$, and Q is $-S(O)_2$.

Scheme 4:

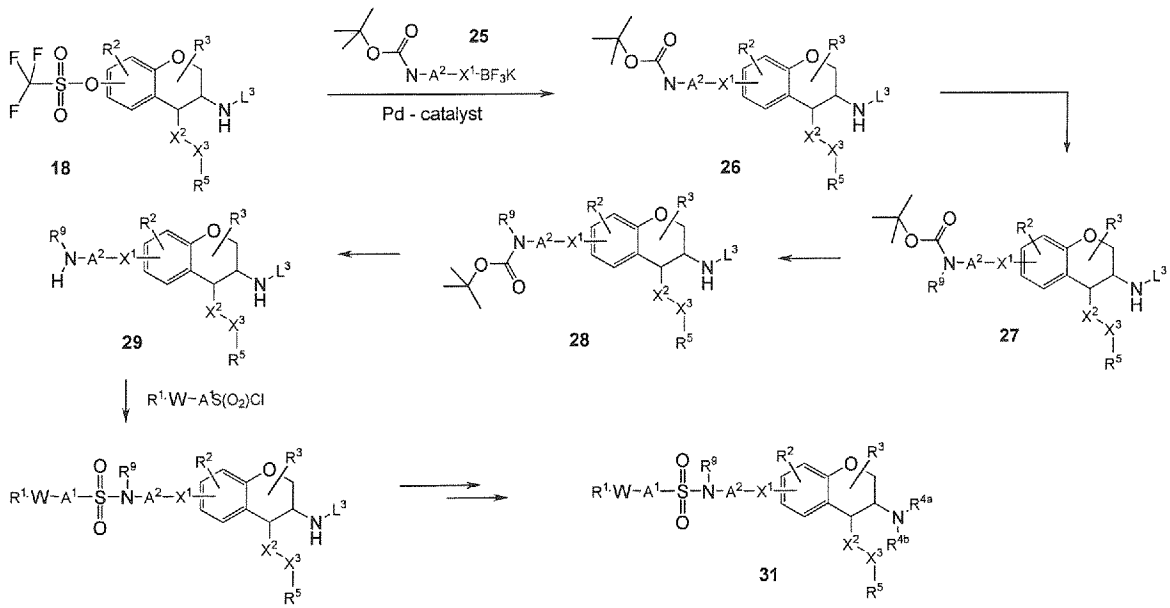


Alternatively to triflate 18, the corresponding nonaflate, bromide or iodide can be used to prepare compound 19.

In scheme 4, the variables L^1, R^1, W, A^1, R^2, R^3, R^{4a}, R^{4b}, R^5, R^9, X^2, X^3 are as defined herein, and L^3 is a suitable protecting group (e.g. L^3 = COOEt or COO^tBu).

The process depicted in scheme 5 is useful for obtaining aminochromanes, wherein X^1 is optionally substituted alkylene, A^2 is optionally substituted alkylene or a bond, Y is $-NR^9-$, and Q is $-S(O)_2$.

Scheme 5:

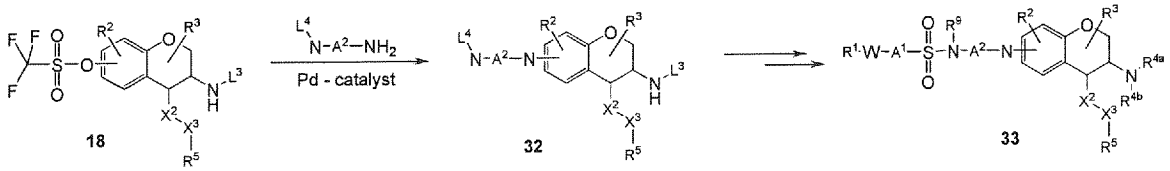


Instead of the trifluoroborate 25, the corresponding 9-borabicyclo[3.3.1]non-9-yl derivative can be used to prepare compound 26.

In scheme 5, the variables R^1, W, A^1, R^2, R^3, R^{4a}, R^{4b}, R^5, R^9, X^2, X^3, A^2 are as defined herein, and L^3 is a suitable protecting group (e.g. L^3 = COOEt, COO^tBu).

The process depicted in scheme 6 is useful for obtaining aminotetralines, wherein X is $-NR^{11}-$, A^2 is optionally substituted alkylene, Y is $-NR^9-$, and Q is $-S(O)_2$.

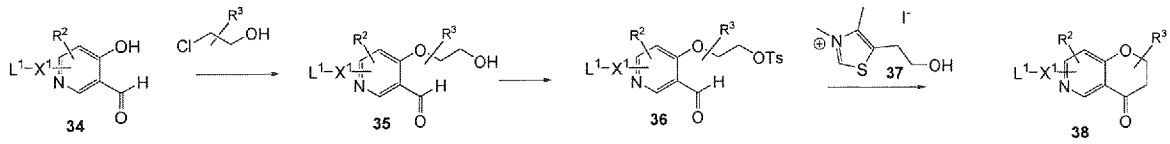
Scheme 6:



In scheme 6, the variables L^3, R^1, W, A^1, R^2, R^3, R^{4a}, R^{4b}, R^5, R^9, X^2, X^3, A^2 are as defined herein, and L^4 is a suitable protecting group.

The process depicted in the following schemes is useful for obtaining compounds of the general formula (I) in which A is a heterocycle.

Scheme 7:

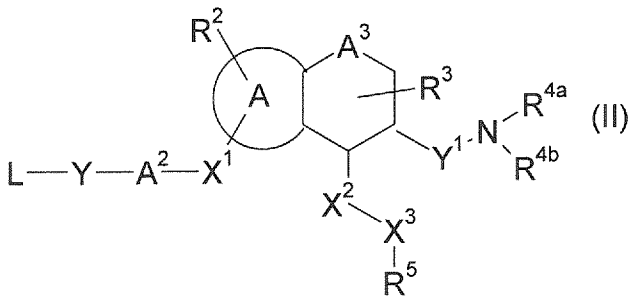


As shown in scheme 7, the compound of general formula 34 readily undergoes substitution with e.g. halogenated ethanol derivatives in presence of a base (e.g. sodium hydroxide) to give the compound of general formula 35. The alkyl hydroxyl group of compound 35 can be transferred into a leaving group (e.g. tosyl) using well known procedures. Compounds of the general formula 36 can be reacted with using N-heterocyclic carbenes as catalyst (e.g. catalyst 37) in presence of a base (e.g. diazabicycloundecen, Org. Lett. 2006, *8*, 4637) to yield compounds of the general formula 38.

In scheme 7, the variables X^1, R^2, R^3 are as defined herein and L^1 a suitable protecting group (e.g. L^1 = Me).

The acid addition salts of the compounds of formula (I) are prepared in a customary manner by mixing the free base with a corresponding acid, optionally in solution in an organic solvent, for example a lower alcohol, such as methanol, ethanol or propanol, an ether, such as methyl tert-butyl ether or diisopropyl ether, a ketone, such as acetone or methyl ethyl ketone, or an ester, such as ethyl acetate.

The aminochromane, aminothiochromane and amino-1,2,3,4-tetrahydroquinoline derivatives of formula (II)



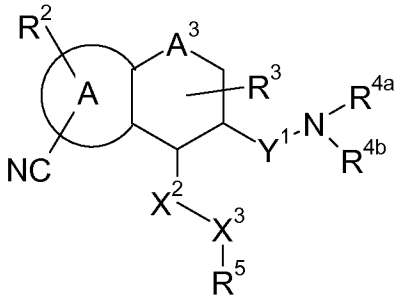
(II)

wherein L is an amino-protecting group, Y is NR^9, and A^2, X^1, A, R^2, A^3, R^3, Y^1, R^{4a}, R^{4b}, X^2, X^3, R^5 are defined as above are useful as intermediates in the preparation of GlyT1 inhibitors, in particular those of formula (I).

Suitable amino-protecting groups are well known in the art such as those described in Protective Groups in Organic Chemistry, ed. J. F. W. McOmie, Plenum Press, 1973; and T. W. Greene & P. G. M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991.

According to a particular embodiment, L is optionally substituted alkylcarbonyl (e.g., tert-butylcarbonyl), optionally substituted arylcarbonyl, optionally substituted arylalkycarbonyl (e.g., benzylcarbonyl), optionally substituted alkoxycarbonyl (e.g., methoxycarbonyl or tert-butyloxycarbonyl), optionally substituted aryloxycarbonyl (e.g. phenoxycarbonyl) or optionally substituted arylalkoxycarbonyl.

Further, the aminochromane, aminothiochromane and amino-1,2,3,4-tetrahydroquinoline derivatives of formula (I) wherein R is –CN, i.e. aminochromane, aminothiochromane and amino-1,2,3,4-tetrahydroquinoline derivatives having the formula (III)



wherein A, R^2, A^3, R^3, Y^1, R^{4a}, R^{4b}, X^2, X^3, R^5 are as defined herein are useful as intermediates in the preparation of GlyT1 inhibitors, in particular those of formula (I).

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 GlyT1c expressing recombinant hGlyT1c_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 µMol, more preferably at a level of IC_{50} < 0.5 µMol, particularly preferably at a level of IC_{50} < 0.2 µMol and most preferably at a level of IC_{50} < 0.1 µMol.

The compounds of formula (I) may exhibit favorable efflux properties which may lead to enhanced oral bioavailability and/or increased brain availability.

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 uselful 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.

According to a further particular embodiment, the disorder is one or more of the following conditions or diseases: schizophrenia or a psychotic disorder including schizophrenia (paranoid, disorganized, catatonic or undifferentiated), schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to a general medical condition and substance- induced psychotic disorder, including both the positive and the negative symptoms of schizophrenia and other psychoses; cognitive disorders including dementia (associated with Alzheimer's disease, ischemia, multi-infarct dementia, trauma, vascular problems or stroke, HIV disease, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jacob disease, perinatal hypoxia, other general medical conditions or substance abuse); delirium, amnestic disorders or cognitive impairment including age related cognitive decline;

anxiety disorders including acute stress disorder, agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder, panic attack, panic disorder, post-traumatic stress disorder, separation anxiety disorder, social phobia, specific phobia, substance-induced anxiety disorder and anxiety due to a general medical condition; substance-related disorders and addictive behaviors (including substance-induced delirium, persisting dementia, persisting amnestic disorder, psychotic disorder or anxiety disorder; tolerance, dependence or withdrawal from substances including alcohol, amphetamines, cannabis, cocaine, hallucinogens, inhalants, nicotine, opioids, phencyclidine, sedatives, hypnotics or anxiolytics); obesity, bulimia nervosa and compulsive eating disorders; bipolar disorders, mood disorders including depressive disorders; depression including unipolar depression, seasonal depression and post-partum depression, premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PDD), mood disorders due to a general medical condition, and substance-induced mood disorders; learning disorders, pervasive developmental disorder including autistic disorder, attention deficit disorders including attention-deficit hyperactivity disorder (ADHD) and conduct disorder; movement disorders, including akinesias and akinetic-rigid syndromes (including Parkinson's disease, drug-induced parkinsonism, postencephalitic parkinsonism, progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration, parkinsonism-ALS dementia complex and basal ganglia calcification), medication-induced parkinsonism (such as neuroleptic-induced parkinsonism, neuroleptic malignant syndrome, neuroleptic-induced acute dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive dyskinesia and medication-induced postural tremor), Gilles de la Tourette's syndrome, epilepsy, muscular spasms and disorders associated with muscular spasticity or weakness including tremors; dyskinesias [including tremor (such as rest tremor, postural tremor and intention tremor), chorea (such as Sydenham's chorea, Huntington's disease, benign hereditary chorea, neuroacanthocytosis, symptomatic chorea, drug-induced chorea and hemiballism), myoclonus (including generalised myoclonus and focal myoclonus), tics (including simple tics, complex tics and symptomatic tics), and dystonia (including generalised dystonia such as iodiopathic dystonia, drug-induced dystonia, symptomatic dystonia and paroxymal dystonia, and focal dystonia such as blepharospasm, oromandibular dystonia, spasmodic dysphonia, spasmodic torticollis, axial dystonia, dystonic writer's cramp and hemiplegic dystonia)]; urinary 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 ellicit 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, neurotropic 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 suboptimal 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 impartment 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 für 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 de-

vices, 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; benziso- thiazolyl-piperazines; triazine such as lamotrigine; dibenzoxazepines, such as loxapine; dihydroindolones, 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 (Glianimon®), 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®), ace-

tophenazine (available under the tradename TINDAL®), prochlorperazine (available under the tradename COMPAZINE®), methotrimeprazine (available under the tradename NOZINAN®), pipotiazine (available under the tradename PIPOTRIL®), ziprasidone, and hoperidone.

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 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.

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 for simultaneous therapeutic administration in the treatment of a neurodegenerative disorder such as Alzheimer Disease. 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 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 acethylcholine receptors, NMDA receptors, amyloid formation, mitochondrial dysfunctions, disease associated calpain activity, neuroinflamation, 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 simultaneous 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, femoxetine, 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, chlomipramine and nortriptiline.

Suitable dopaminergic antidepressants which may be used in combination with a compound of the invention include bupropion and amineptine.

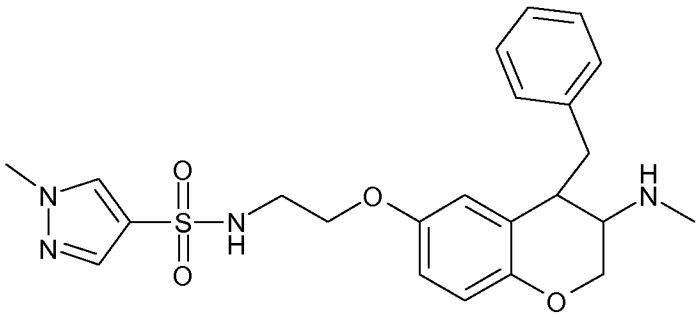
Suitable anticonvulsant agents which may be used in combination of the compounds of the invention include for example divalproex, carbamazepine and diazepam.

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).

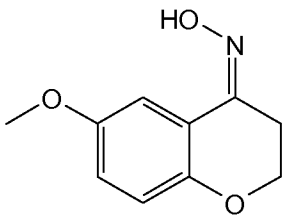
Preparation Examples

Example 1: *cis*-N-(2-{[-4-Benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]oxy}ethyl)-1-methyl-1H-pyrazole-4-sulfonamide hydrochloride and *trans*-N-(2-{[-4-benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]oxy}ethyl)-1-methyl-1H-pyrazole-4-sulfonamide hydrochloride



ClH

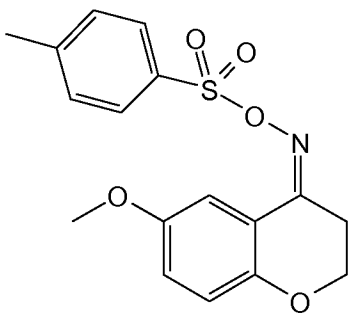
1.1 6-Methoxychroman-4-one oxime



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.

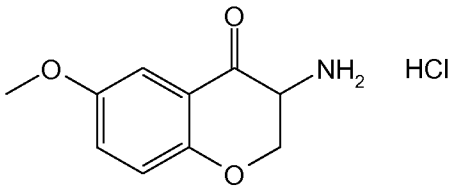
ESI-MS $[M+H^+]$ = 194 Calculated for $C_{10}H_{11}NO_3$ = 193.

1.2 6-Methoxychroman-4-one O-tosyl oxime



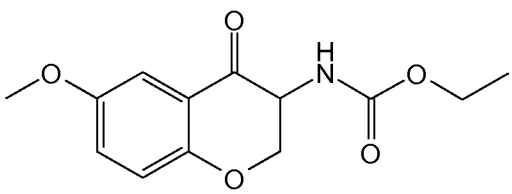
5.68 g (29.4 mmol) of 6-methoxychroman-4-one oxime were dissoled under argon atmosphere in 30 ml of dry pyridine. At 0°C 6.05 g (31.8 mmol) of 4-methylbenzene-1-sulfonyl chloride were added in small portions over 40 min. The mixture was stirred at 0 °C for an additional hour and then warmed to room temperature and stirred over night. The mixture was poured onto 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 $C_{17}H_{17}NO_5S$ = 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 water and phases were separated. The organic phase was extracted with aqueous hudrogen 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 wass 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

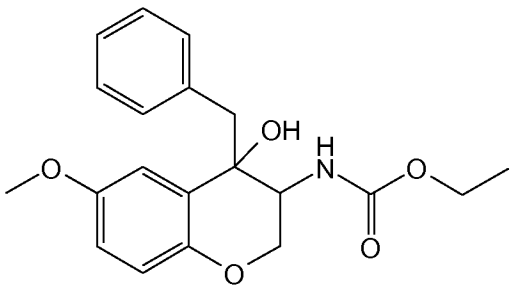


2.82 g (12.3 mmol) of 6-methoxy-4-oxochroman-3-aminium chloride were dissolved in tetrahydrofuran under nitrogen atmosphere and cooled to 0 °C with an ice bath. Diisopro-

pylethylamine 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 $MgSO_4$, and concentrated in vacuo to give 3.5 g (13.2 mmol, quant.) of crude material.

ESI-MS $[M+H^+]$ = 265 Calculated for $C_{13}H_{15}NO_5$ = 266.

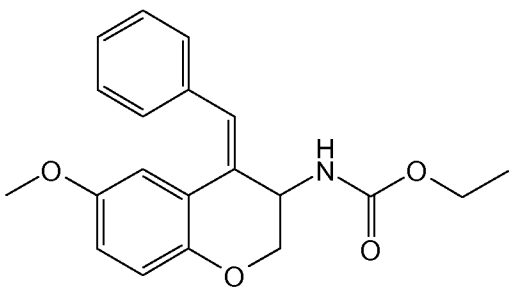
1.5 Ethyl 4-benzyl-4-hydroxy-6-methoxychroman-3-ylcarbamate



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 $MgSO_4$, and concentrated in vacuo to give 6.87 g (9.1 mmol, quant.) of crude material.

ESI-MS $[M+Na^+]$ = 380 Calculated for $C_{20}H_{23}NO_5$ = 357.

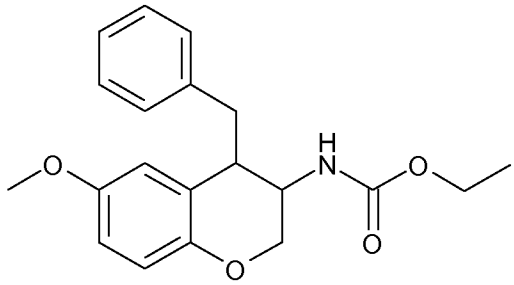
1.6 Ethyl 4-benzylidene-6-methoxychroman-3-ylcarbamate



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 HCl 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 $MgSO_4$ 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 $C_{20}H_{21}NO_4$ = 340.

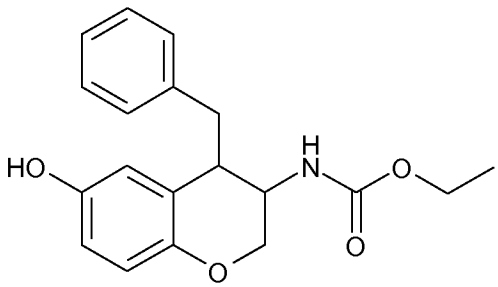
1.7 Ethyl 4-benzyl-6-methoxychroman-3-ylcarbamate



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) 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 vacuuo to remove EtOH. The aqueous concentrate was extracted with ethyl acetate (2x). The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated to yield 3.2 g (9.3 mmol, quant.) of the crude product.

ESI-MS [M+H$^+$] = 342 Calculated for $C_{20}H_{23}NO_4$ = 341.

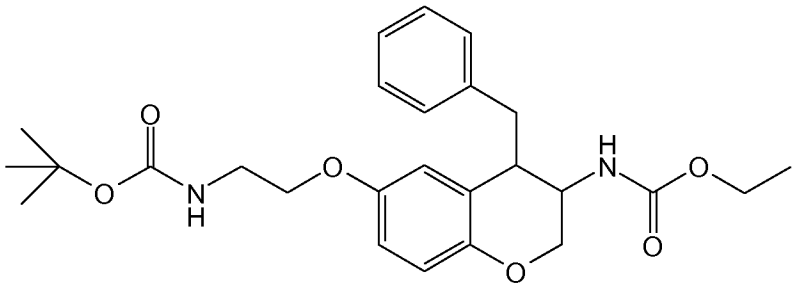
1.8 Ethyl 4-benzyl-6-hydroxychroman-3-ylcarbamate



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 hydrogencarbonat 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 $MgSO_4$ 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 $C_{19}H_{21}NO_4$ = 327.

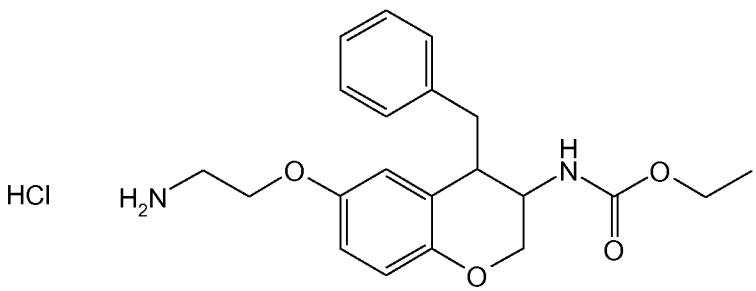
1.9 [4-Benzyl-6-(2-tert-butoxycarbonylamino-ethoxy)-chroman-3-yl]-carbamic acid ethyl ester



150 mg (3.75 mmol, 60 % in mineral oil) of sodium hydride were suspended under nitrogen atmosphere in 2 m dry dimethyl acetamide. 488 mg (1.5 mmol) of ethyl 4-benzyl-6-hydroxychroman-3-ylcarbamate dissolved in 8 ml dry dimethyl acetamide were added dropwise at room temperature and stiired for 1 h. Then 1.0 g (4.47 mmol) of tert-butyl 2-bromoethylcarbamate dissolved in 2 ml acetate amide were added slowly. The reaction mixture was allowed to warm to room temperature and stirred for 84 h. Then additional 50 mg (1.4 mmol) sodium hydride were added and the mixture was stirred for 30 min before additional 350 mg of tert-butyl 2-bromoethylcarbamate were added and the mixture was stirred for additional 72 h. The reaction mixture was poured onto diluted sodium hydrogencarbonate solution and extracted with ether (2x). The combined organic phases were washed with water (2x), dried over $MgSO_4$ and concentrated (1.5 g of crude). The crude material was purified by flash chromatography to give 587 mg (1.25 mmol, 84 %) of the desired product.

ESI-MS [M+Na^+] = 493 Calculated for $C_{26}H_{34}N_2O_6$ = 327.

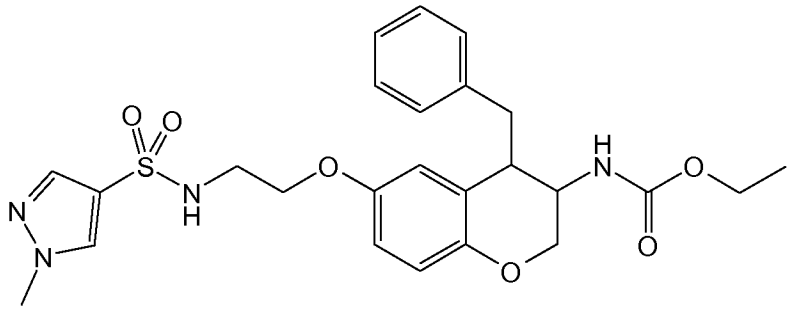
1.10 Ethyl 6-(2-aminoethoxy)-4-benzylchroman-3-ylcarbamate hydrochloride



487 mg (1.04 mmol) of [4-benzyl-6-(2-tert-butoxycarbonylamino-ethoxy)-chroman-3-yl]-carbamic acid ethyl ester were dissolved in 10 ml methylene dichloride and 2 ml of a solution of hydrogen chloride in isopropanol (5-6 N) were added and the mixture was stirred over night at room temperature. The reaction mixture was warmed to 40 °C, stirred for additional 45 min, and concentrated. The residue was dissolved in water and washed with ether. The aqueous phase was concentrated and the residue co-distilled with toluene to give 463 mg (1.14 mmol, quant.) of the desired product.

ESI-MS [M+H$^+$] = 371 Calculated for $C_{21}H_{26}N_2O_4$ = 370.

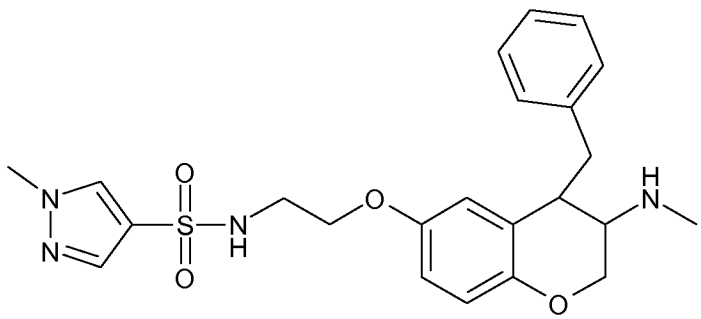
1.11 Ethyl 4-benzyl-6-(2-(1-methyl-1H-pyrazole-4-sulfonamido)ethoxy)chroman-3-ylcarbamate



100 mg (0.25 mmol) of 2-(4-benzyl-3-(ethoxycarbonylamino)chroman-6-yloxy)ethanaminium chloride were dissolved in 5 ml methylene dichloride. Then, 95 mg (0.79 mmol) dimethyl aminopyridine and 54 mg (0.30 mmol) 1-methyl-1H-pyrazole-4-sulfonyl chloride were added. The reaction mixture was stirred at room temperature over night. The mixture was concentrated in vacuo and the residue was dissolved in ethylacetate and water. The phases were separated. The organic phase was washed with saturated ammonium chloride solution (2x), dried over $MgSO_4$ and concentrated (127 mg crude). The crude material was purified by column chromatography to give 118 mg (0.23 mmol, 93 %) of the desired product.

ESI-MS [M+H$^+$] = 515 Calculated for $C_{25}H_{30}N_4O_6S$ = 514.

1.12 *cis*-N-(2-{[-4-Benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]oxy}ethyl)-1-methyl-1H-pyrazole-4-sulfonamide hydrochloride and *trans*-N-(2-{[-4-benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]oxy}ethyl)-1-methyl-1H-pyrazole-4-sulfonamide hydrochloride



ClH

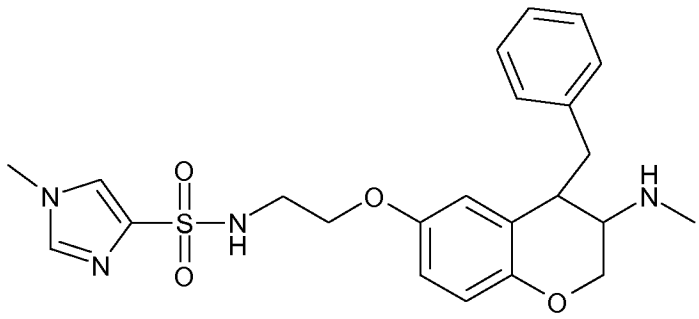
118 mg (0.23 mmol) of ethyl 4-benzyl-6-(2-(1-methyl-1H-pyrazole-4-sulfonamido)ethoxy)chroman-3-ylcarbamate were dissolved in 5 ml tetrahydrofurane under nitrogen atmosphere. Then, 0.7 ml (0.70 mmol) of lithiumaluminum hydride (1M in tetrahydrofurane) were added. The reaction mixture was heated to reflux and stirred for 2

h. The mixture was allowed to cool to room temperature and excess lithiumaluminum hydride were quenched by adding methanol. The solvent was removed and the residue was dissolved in ethyl acetate and sodium hydrogencarbonate solution. The phases were separated and the aqueous layer was extracted with ethyl acetate (2x). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated (105 mg crude). The crude material was purified by column chromatography to give 53 mg (0.11 mmol, 47 %) of cis diastereomer and additional 15 mg (0.03 mmol, 13 %) of trans diastereomer.

cis-isomer: ESI-MS [M+Na^+] = 457 Calculated for $C_{22}H_{26}N_4O_4S$ = 442.

trans-isomer: ESI-MS [M+Na^+] = 457 Calculated for $C_{22}H_{26}N_4O_4S$ = 442.

Example 2: *cis*-N-(2-{[-4-Benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]oxy}ethyl)-1-methyl-1H-imidazole-4-sulfonamide and *trans*-N-(2-{[-4-benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]oxy}ethyl)-1-methyl-1H-imidazole-4-sulfonamide

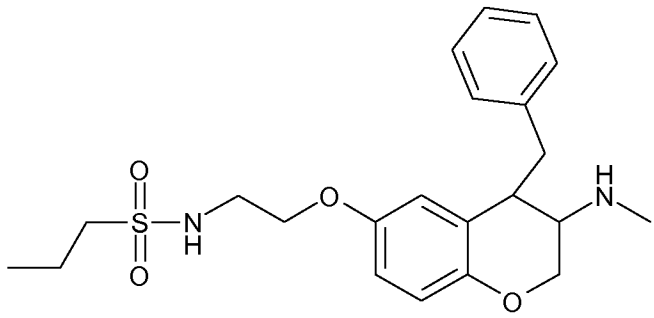


Cis-N-(2-{[-4-Benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]oxy}ethyl)-1-methyl-1H-imidazole-4-sulfonamide and *trans*-N-(2-{[-4-benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]oxy}ethyl)-1-methyl-1H-imidazole-4-sulfonamide were prepared in analogy to example 1.

cis-isomer: ESI-MS [M+H^+] = 457 Calculated for $C_{22}H_{26}N_4O_4S$ = 456.

trans-isomer: ESI-MS [M+H^+] = 457 Calculated for $C_{22}H_{26}N_4O_4S$ = 456.

Example 3: *cis*-N-(2-{[-4-Benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]oxy}ethyl)propane-1-sulfonamide and *trans*-N-(2-{[-4-benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]oxy}ethyl)propane-1-sulfonamide

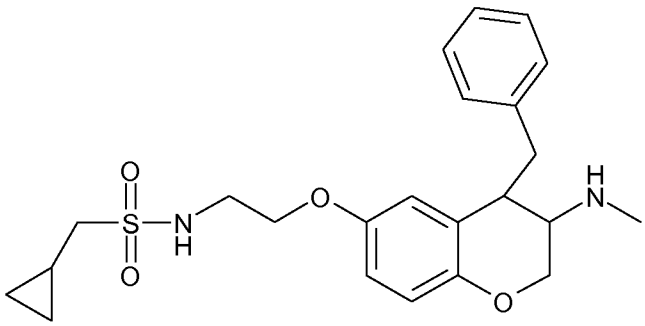


Cis-N-(2-{[-4-Benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]oxy}ethyl)propane-1-sulfonamide and *trans*-N-(2-{[-4-benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]oxy}ethyl)propane-1-sulfonamide were prepared in analogy to example 1.

cis-isomer: ESI-MS $[M+H^+]$ = 419 Calculated for $C_{22}H_{30}N_2O_4S$ = 418.

trans-isomer: ESI-MS $[M+H^+]$ = 419 Calculated for $C_{22}H_{30}N_2O_4S$ = 418.

Example 4: *cis*-N-(2-{[-4-Benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]oxy}ethyl)-1-cyclopropylmethanesulfonamide and *trans*-N-(2-{[-4-benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]oxy}ethyl)-1-cyclopropylmethanesulfonamide



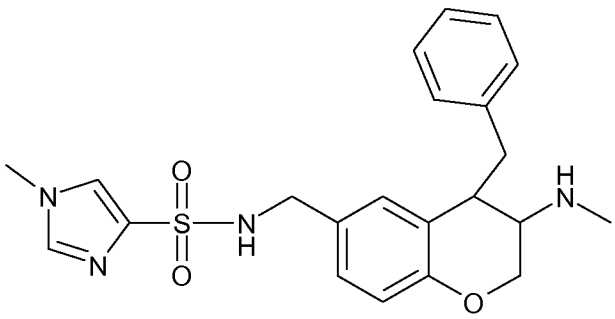
cis-N-(2-{[-4-Benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]oxy}ethyl)-1-cyclopropylmethanesulfonamide and *trans*-N-(2-{[-4-benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]oxy}ethyl)-1-cyclopropylmethanesulfonamide were prepared in analogy to example 1.

cis-isomer: ESI-MS $[M+H^+]$ = 431 Calculated for $C_{23}H_{30}N_2O_4S$ = 430.

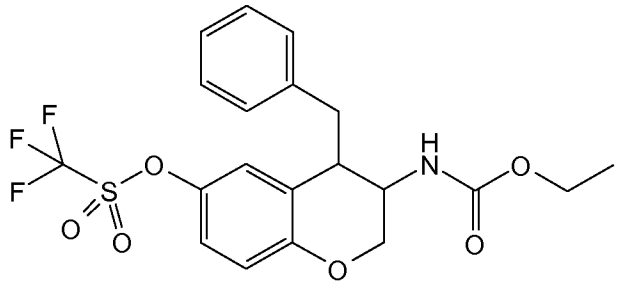
trans-isomer: ESI-MS $[M+H^+]$ = 431 Calculated for $C_{23}H_{30}N_2O_4S$ = 430.

Example 5:

Example 5: *cis*-1-Methyl-1H-imidazole-4-sulfonic acid (4-benzyl-3-methylamino-chroman-6-ylmethyl)-amide and *trans*-1-Methyl-1H-imidazole-4-sulfonic acid (4-benzyl-3-methylamino-chroman-6-ylmethyl)-amide

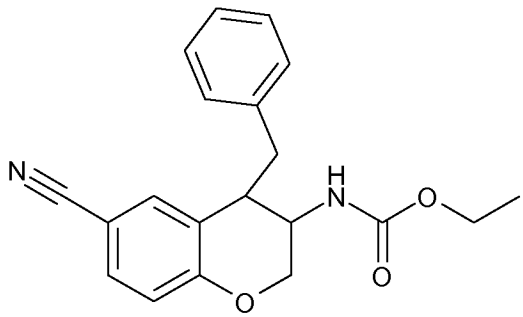


5.1 4-Benzyl-3-(ethoxycarbonylamino)chroman-6-yl trifluoromethanesulfonate



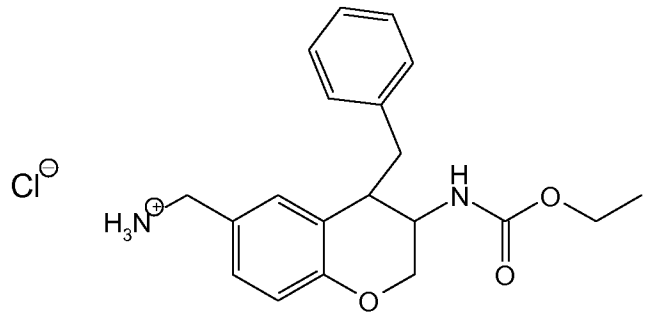
1.23 g (3.7 mmol) of ethyl 4-benzyl-6-hydroxychroman-3-ylcarbamate under nitrogen atmosphere were dissolved in 50 ml of methylene dichloride and 0.61 ml (7.48 mmol) pyridine were added. At 0°C 0.76 ml (4.5 mmol) trifluoromethanesulfonic anhydride were added. The reaction mixture was stirred at 0 °C for 1 h. The mixture was quenched with iced water and acidified uusing aqueous hydrogen chloride (1 M).The phases were separated and the aqueous phase was extracted with methylene dichloride. The combined organic layers dried over $MgSO_4$ and the solvent was evaporated. The crude material was purified by flash chromatography to give 1.61 g (3.5 mmol, 94%) of the desired product.
ESI-MS $[M+H^+]$ = 460 Calculated for $C_{20}H_{20}F_3NO_6S$ = 459.

5.2 Ethyl 4-benzyl-6-cyanochroman-3-ylcarbamate



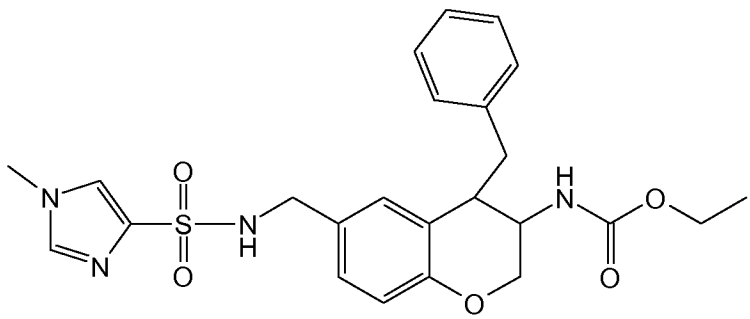
1.25 g (2.71 mmol) of 4-benzyl-3-(ethoxycarbonylamino)chroman-6-yl trifluoromethanesulfonate were dissolved in 25 ml dimethyl formamide under nitrogen atmosphere. 250 mg (2.13 mmol) of dicyanozinc, 84 mg (0.08 mmol) tris(dibenzylideneacetone)dipalladium (0) chloroform adduct , and 90 mg (0.16 mmol) 1,1-bis(diphenylphosphino)ferrocene were added. The reaction mixture was heated to 120 °C and stirred for 1 hour. The reaction mixture was cooled to room temperature and poured on water. The aqueous layer was extracted with diethyl ether (2x). The combined organic phases were washed with water, dried over $MgSO_4$ and concentrated (945 mg crude). The crude material was purified by flash chromatography to give 716 mg (2.13 mmol, 79 %) of the desired product.
ESI-MS $[M+H^+]$ = 337 Calculated for $C_{20}H_{20}N_2O_3$ = 336.

5.3 4-Benzyl-3-(ethoxycarbonylamino)chroman-6-yl)methanaminium chloride



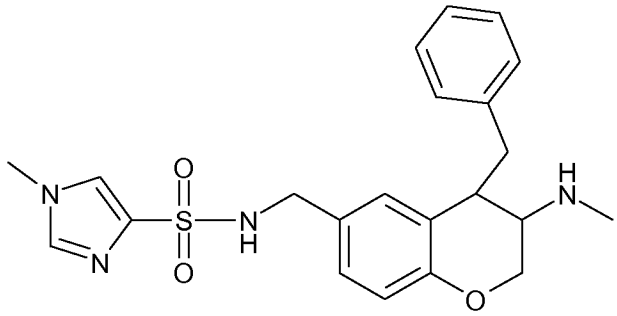
716 mg (2.13 mmol) of ethyl 4-benzyl-6-cyanochroman-3-ylcarbamate were dissolved in 20 ml tetrahydrofurane under nitrogene atmosphere and 222 ml (2.34 mmol) borane methyl sulfide complex were added. The reaction mixture was heated to reflux and stirred for 2 hours. The reaction mixture was cooled to room temperature and 15 ml (1.25 M, 18.75 mmol) of a solution of hydrogene chloride in ethanol were added. The mixture was stirred until the gas evolution ceased and concentrated. The residue was dissolved in methanol and co-distilled with toluene (2x). The residue was then dissolved in methylene chloride and concentrated. Small amounts of diethyl ether were added to the foam. After sedimentation of the solids the ether solution was decanted and the solid residue dried in vacuo to yield 804 mg (2.13 mmol, 100 %) of crude material that was directly used in the next step.
ESI-MS $[M+Na^+]$ = 363 Calculated for $C_{20}H_{24}N_2O_3$ = 340.

5.4 Ethyl 4-benzyl-6-((1-methyl-1H-imidazole-4-sulfonamido)methyl)chroman-3-ylcarbamate



50 mg (0.13 mmol) of 4-benzyl-3-(ethoxycarbonylamino)chroman-6-yl)methanaminium chloride were dissolved in 2 ml methylene dichloride. Then, 63 mg (0.52 mmol) dimethyl aminopyridine and 28 mg (0.16 mmol) 1-methyl-1H-imidazole-4-sulfonyl chloride were added and the reaction mixture was stirred at room temperature for 45 minutes. The mixture was concentrated in vacuo and the residue was dissolved in ethylacetate and water. The phases were separated. The organic phase was washed with saturated ammonium chloride solution (2x), dried over $MgSO_4$ and concentrated (63 mg crude, 0.13 mmol, 98 %).
ESI-MS $[M+H^+]$ = 485 Calculated for $C_{24}H_{28}N_4O_5S$ = 484.

5.5 *cis*-1-Methyl-1H-imidazole-4-sulfonic acid (4-benzyl-3-methylamino-chroman-6-ylmethyl)-amide and *trans*-1-Methyl-1H-imidazole-4-sulfonic acid (4-benzyl-3-methylamino-chroman-6-ylmethyl)-amide

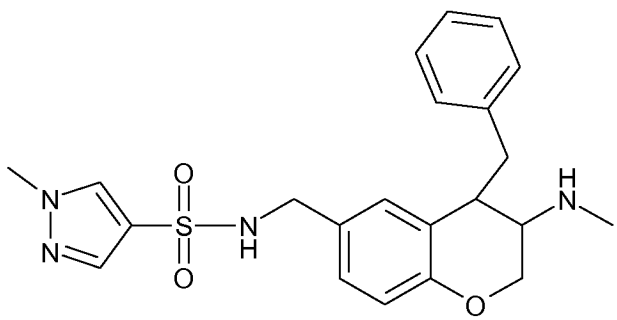


63 mg (0.13 mmol) of ethyl 4-benzyl-6-((1-methyl-1H-imidazole-4-sulfonamido)methyl)-chroman-3-ylcarbamate were dissolved in 3 ml tetrahydrofurane under nitrogen atmosphere. Then, 0.5 ml (0.52 mmol) of lithiumaluminum hydride (1M in tetrahydrofurane) were added. The reaction mixture was heated to reflux and stirred for 1 hour. Additional 0.2 ml (0.21 mmol) of lithiumaluminum hydride (1M in tetrahydrofurane) were added and the mixture stirred at 65 °C for 1 hour. The mixture was allowed to cool to room temperature and excess lithiumaluminum hydride was quenched by adding methanol. The solvent was removed and the residue was dissolved in ethyl acetate and sodium hydrogencarbonate solution. The phases were separated and the aqueous layer was extracted with ethyl acetate (1x) and methylene dichloride. The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated (53 mg crude). The crude material was purified by column chromatography to give 6 mg (0.013 mmol, 10 %) of cis diastereomer and additional 5 mg (0.011 mmol, 8 %) of trans diastereomer.

cis-isomer: ESI-MS $[M+H^+]$ = 427 Calculated for $C_{22}H_{26}N_4O_3S$ = 426.

trans-isomer: ESI-MS $[M+H^+]$ = 427 Calculated for $C_{22}H_{26}N_4O_3S$ = 426.

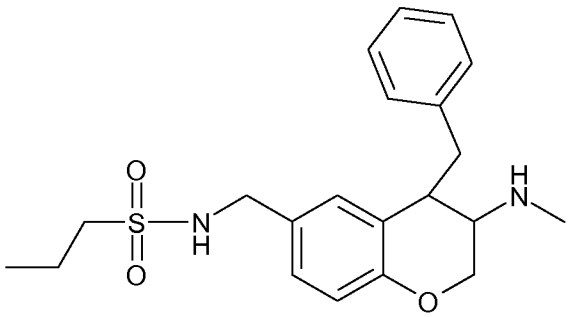
Example 6: *cis*-N-{[4-benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]methyl}-1-methyl-1H-pyrazole-4-sulfonamide and *trans*-N-{[-4-benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]methyl}-1-methyl-1H-pyrazole-4-sulfonamide



Cis-N-{[-4-Benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]methyl}-1-methyl-1H-pyrazole-4-sulfonamide and *trans*-N-{[-4-benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]methyl}-1-methyl-1H-pyrazole-4-sulfonamide were prepared in analogy to example 5

cis-isomer: ESI-MS $[M+H^+]$ = 427 Calculated for $C_{22}H_{26}N_4O_3S$ = 426.
trans-isomer: ESI-MS $[M+H^+]$ = 427 Calculated for $C_{22}H_{26}N_4O_3S$ = 426.

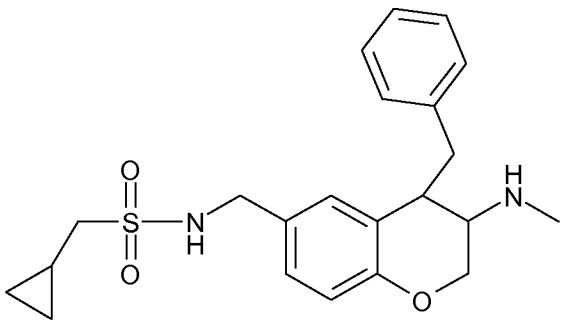
Example 7: *cis*-N-{[4-Benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]methyl}propane-1-sulfonamide and *trans*-N-{[4-benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]methyl}propane-1-sulfonamide



Cis-N-{[4-Benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]methyl}propane-1-sulfonamide and *trans*-N-{[4-benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]methyl}propane-1-sulfonamide were prepared in analogy to example 5.

cis-isomer: ESI-MS $[M+H^+]$ = 389 Calculated for $C_{21}H_{28}N_2O_3S$ = 388.
trans-isomer: ESI-MS $[M+H^+]$ = 389 Calculated for $C_{21}H_{28}N_2O_3S$ = 388.

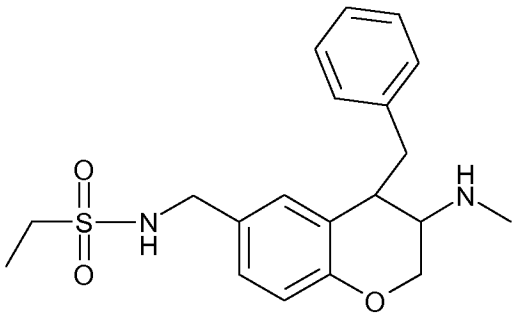
Example 8: *cis*-N-{[4-Benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]methyl}-1-cyclopropylmethanesulfonamide and *trans*-N-{[4-benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]methyl}-1-cyclopropylmethanesulfonamide



Cis-N-{[4-Benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]methyl}-1-cyclopropylmethanesulfonamide and *trans*-N-{[4-benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]methyl}-1-cyclopropylmethanesulfonamide were prepared in analogy to example 5.

cis-isomer: ESI-MS [M+H$^+$] = 401 Calculated for $C_{22}H_{28}N_2O_3S$ = 400.
trans-isomer: ESI-MS [M+H$^+$] = 401 Calculated for $C_{22}H_{28}N_2O_3S$ = 400.

Example 9: *cis*-N-{[4-Benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]methyl}ethanesulfonamide and *trans*-N-{[4-benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]methyl}ethanesulfonamide

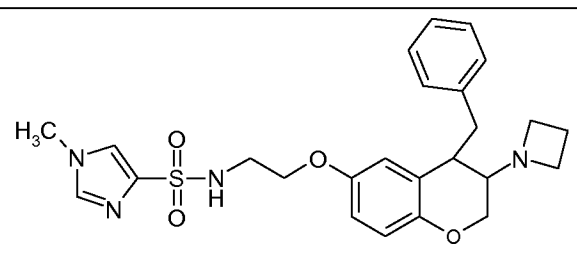


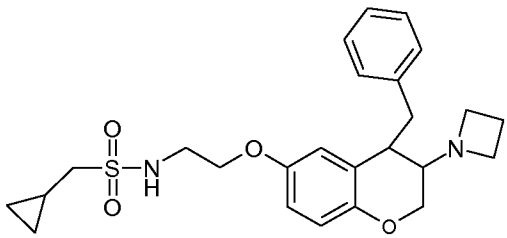
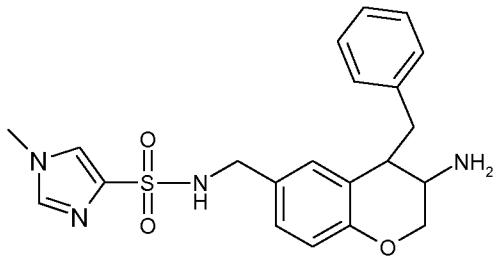
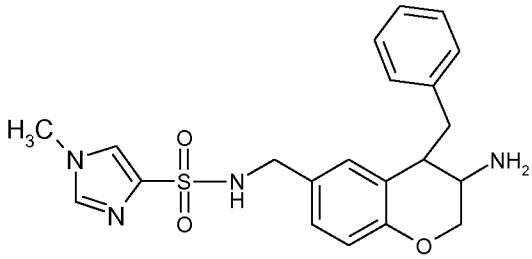
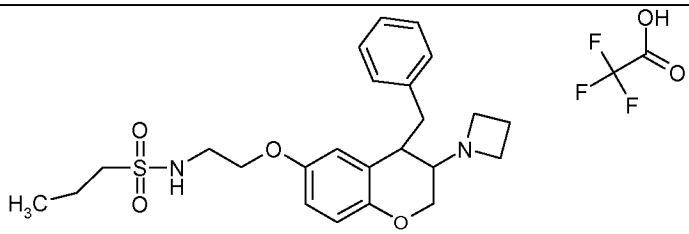
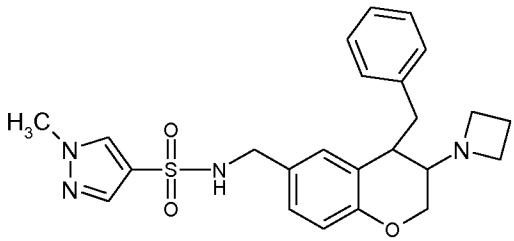
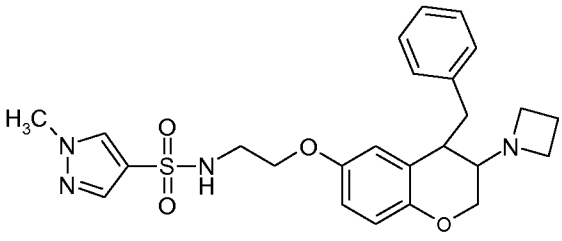
Cis-N-{[4-Benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]methyl}ethanesulfonamide and *trans*-N-{[4-benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]methyl}ethanesulfonamide were prepared in analogy to example 5.
cis-isomer: ESI-MS [M+H$^+$] = 375 Calculated for $C_{20}H_{26}N_2O_3S$ = 374.
trans-isomer: ESI-MS [M+H$^+$] = 375 Calculated for $C_{20}H_{26}N_2O_3S$ = 374.

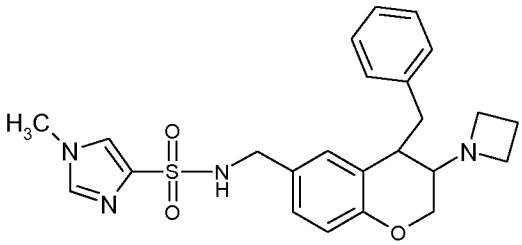
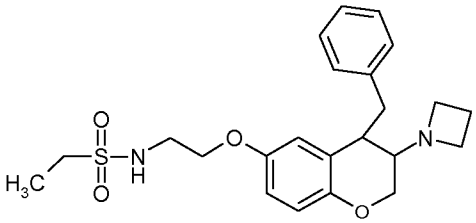
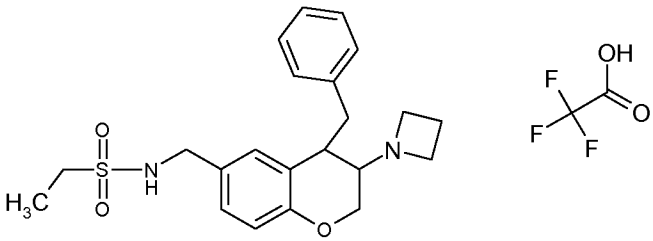
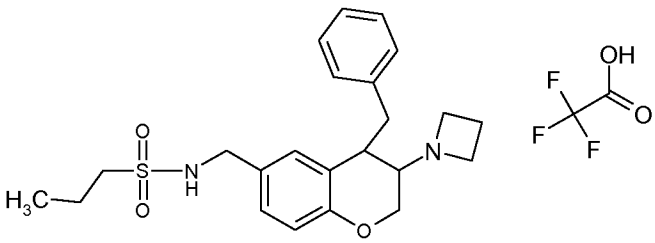
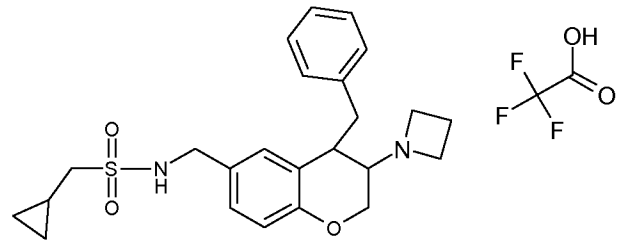
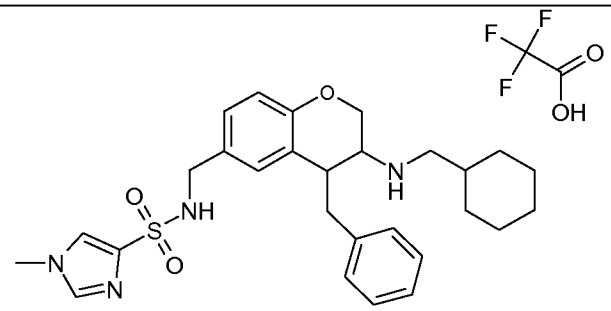
The following compounds were obtained using the procedures described herein and in WO2010/092180 (which is incorporated herein in its entirety by reference). Commercially available 2,2-dimethyl-6-methoxychroman-4-one was used as starting material for exmples 73-80.

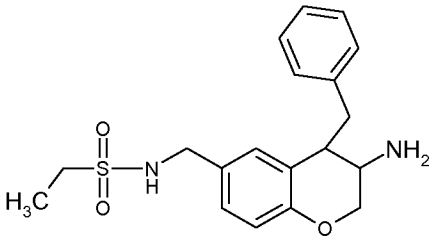
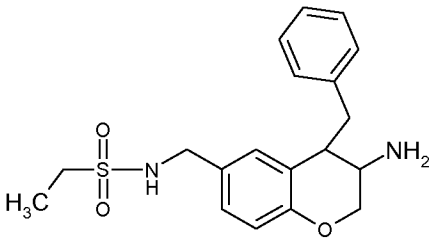
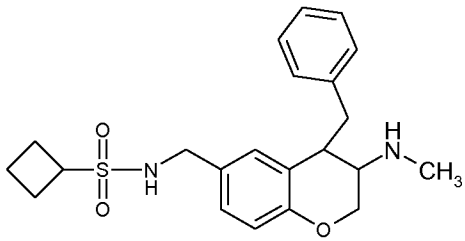
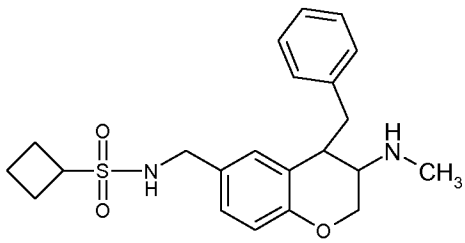
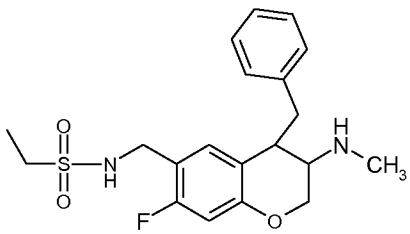
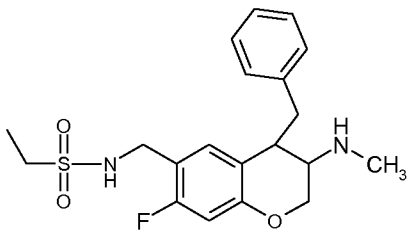
Compound 79 was prepared by separation of the racemic mixture obtained in example 9 through chiral chromatography on Chiralpak AD-H (n-Heptan / EtOH 70:30 + 0,1%Et_3N) and isolation of the isomer as the second eluting peak.

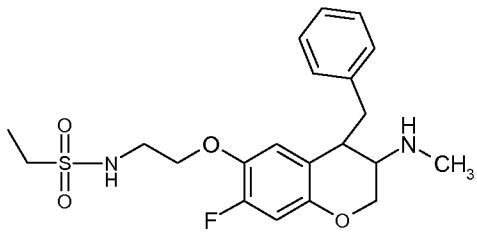
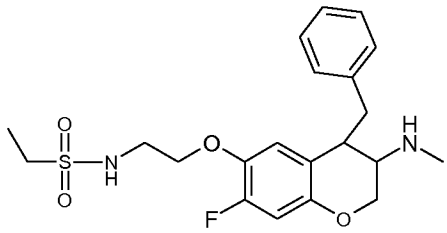
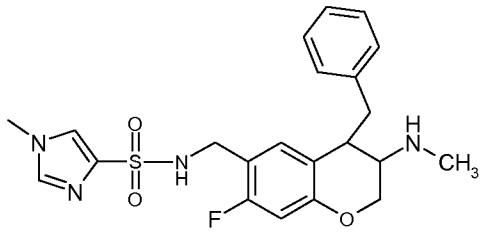
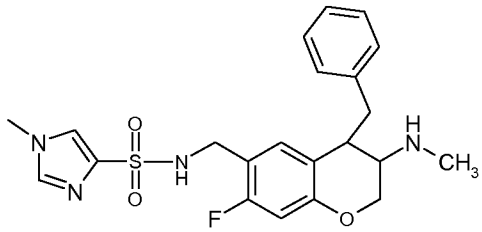
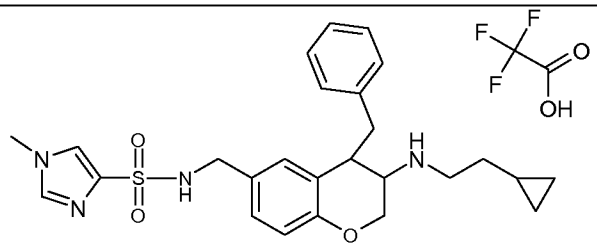
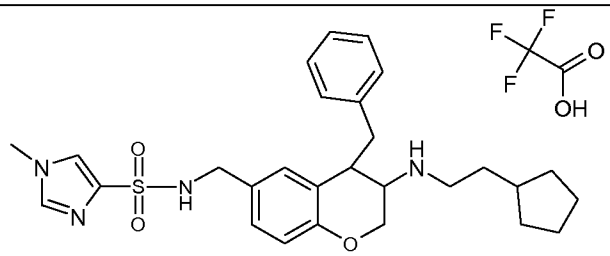
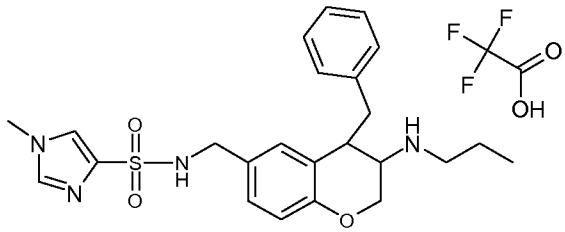
Compounds 80 was prepared by separation of the racemic mixture obtained in example 10 through chiral chromatography on Chirapak AD-H (n-Heptan / EtOH 50:50 + 0,1%Et_3N) and isolation of the isomer as the second eluting peak.

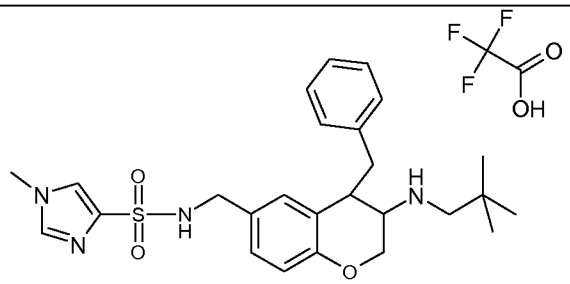
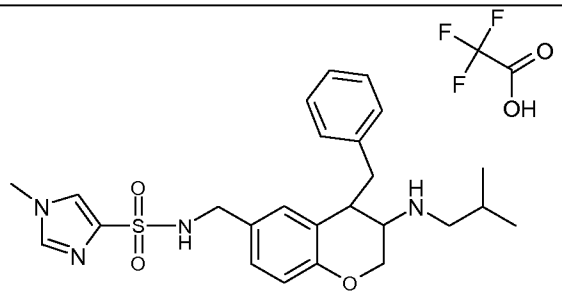
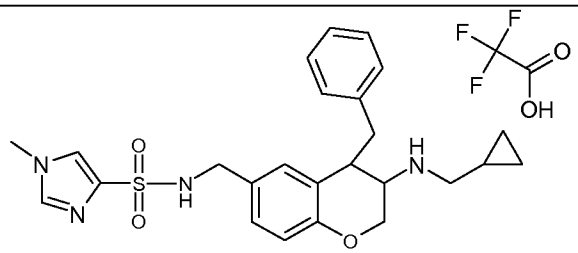
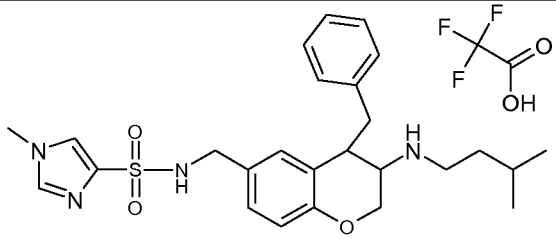
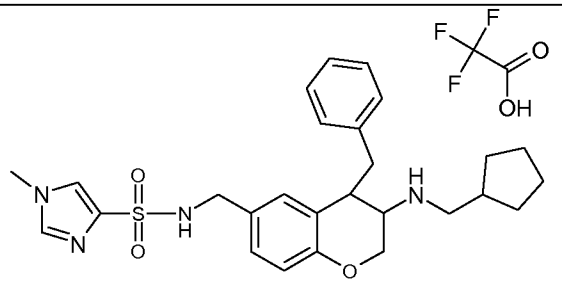
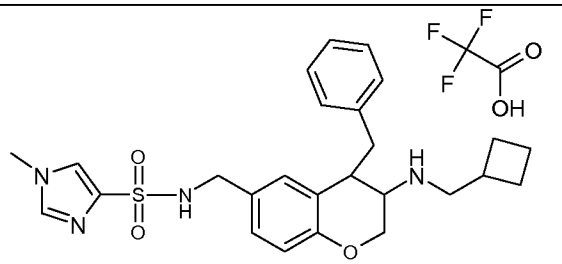
10		*cis*-1-Methyl-1H-imidazole-4-sulfonic acid [2-(3-azetidin-1-yl-4-benzyl-chroman-6-yloxy)-ethyl]-amide

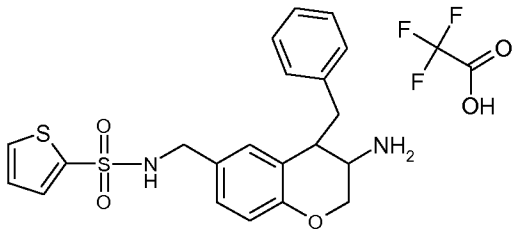
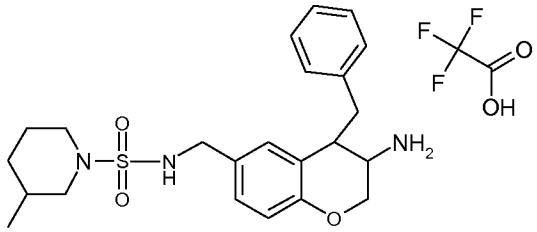
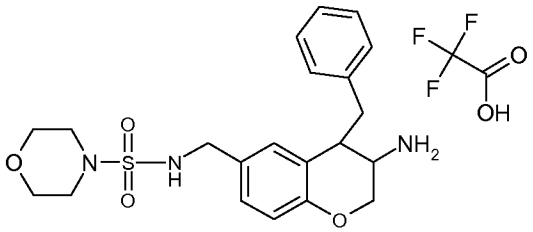
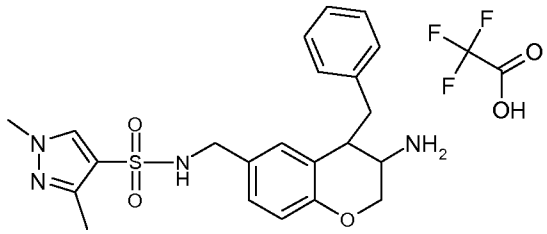
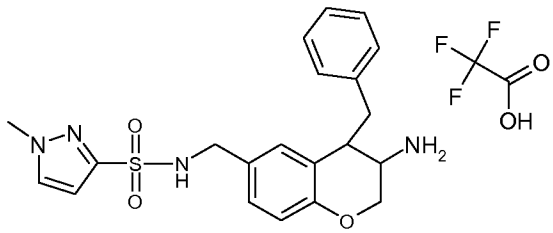
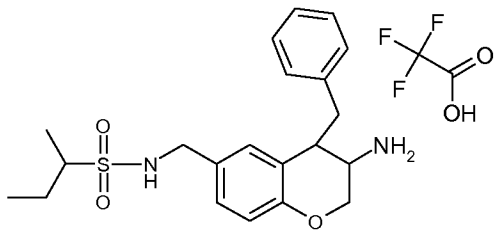
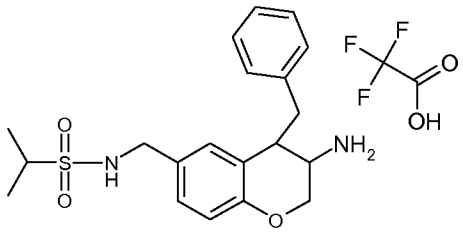
11		*cis*-N-[2-(3-Azetidin-1-yl-4-benzyl-chroman-6-yloxy)-ethyl]-C-cyclopropyl-methanesulfonamide
12		*cis*-1-Methyl-1H-imidazole-4-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide
13		*trans*-1-Methyl-1H-imidazole-4-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide
14		*cis*-Propane-1-sulfonic acid [2-(3-azetidin-1-yl-4-benzyl-chroman-6-yloxy)-ethyl]-amide; trifluoro-acetic acid salt
15		*cis*-1-Methyl-1H-pyrazole-4-sulfonic acid (3-azetidin-1-yl-4-benzyl-chroman-6-ylmethyl)-amide
16		*cis*-1-Methyl-1H-pyrazole-4-sulfonic acid [2-(3-azetidin-1-yl-4-benzyl-chroman-6-yloxy)-ethyl]-amide

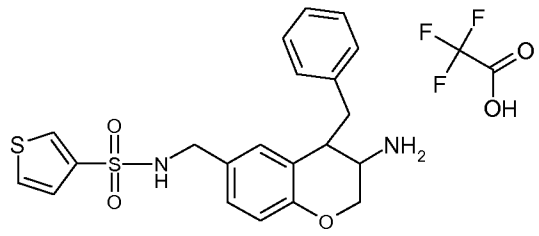
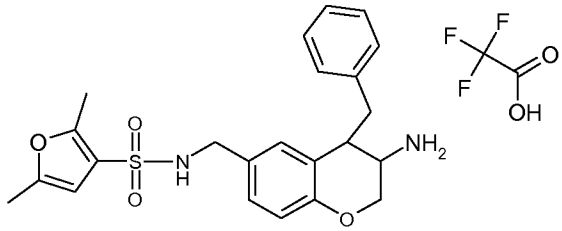
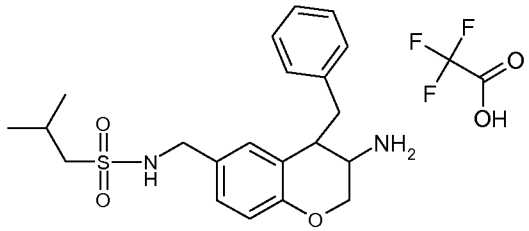
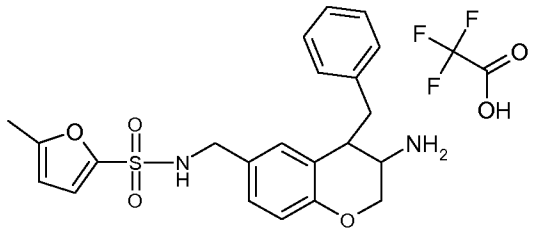
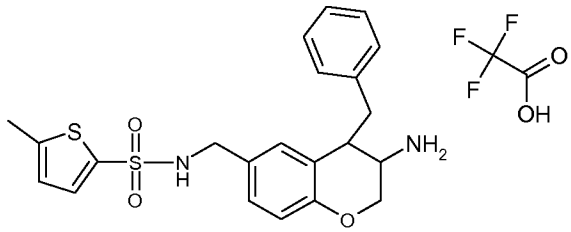
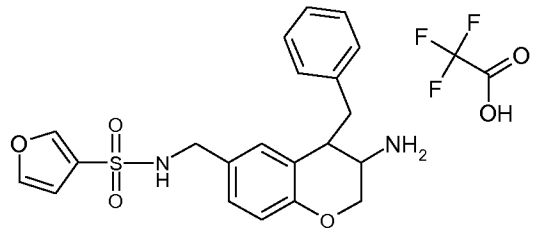
17		*cis*-1-Methyl-1H-imidazole-4-sulfonic acid (3-azetidin-1-yl-4-benzyl-chroman-6-ylmethyl)-amide
18		*cis*-Ethanesulfonic acid [2-(3-azetidin-1-yl-4-benzyl-chroman-6-yloxy)-ethyl]-amide
19		Ethanesulfonic acid (3-azetidin-1-yl-4-benzyl-chroman-6-ylmethyl)-amide; trifluoro-acetic acid salt
20		Propane-1-sulfonic acid (3-azetidin-1-yl-4-benzyl-chroman-6-ylmethyl)-amide; trifluoro-acetic acid salt
21		N-(3-Azetidin-1-yl-4-benzyl-chroman-6-ylmethyl)-C-cyclopropyl-methane-sulfonamide; trifluoro-acetic acid salt
22		*cis*-1-Methyl-1H-imidazole-4-sulfonic acid [4-benzyl-3-(cyclohexylmethyl-amino)-chroman-6-lmethyl]-amide; trifluoro-acetic acid salt

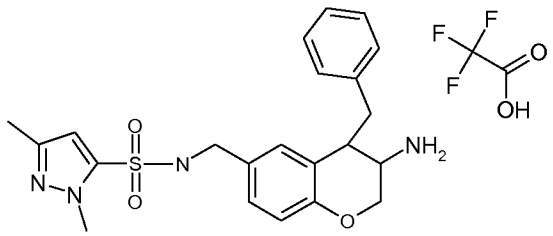
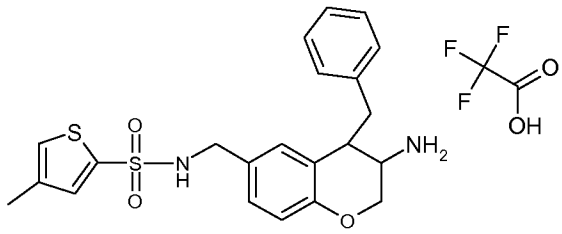
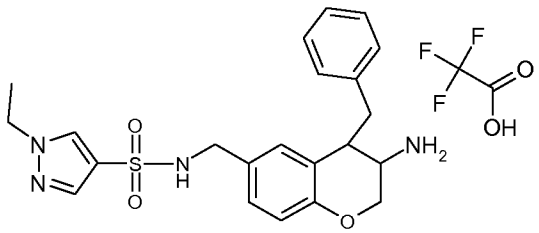
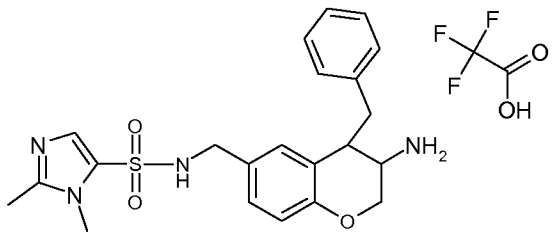
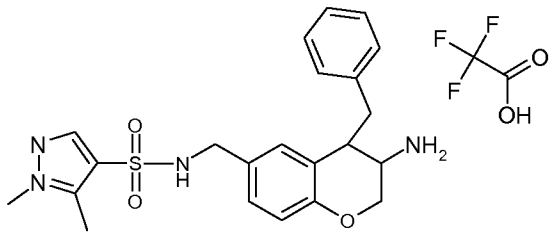
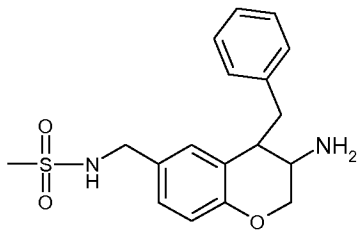
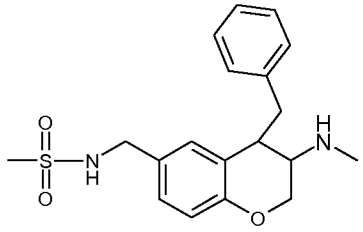
23		*cis*-Ethanesulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide
24		*trans*-Ethanesulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide
25		*cis*-Cyclobutanesulfonic acid (4-benzyl-3-methylamino-chroman-6-ylmethyl)-amide
26		*trans*-Cyclobutanesulfonic acid (4-benzyl-3-methylamino-chroman-6-ylmethyl)-amide
27		cis-Ethanesulfonic acid (-4-benzyl-7-fluoro-3-methylamino-chroman-6-ylmethyl)-amide
28		trans-Ethanesulfonic acid (-4-benzyl-7-fluoro-3-methylamino-chroman-6-ylmethyl)-amide

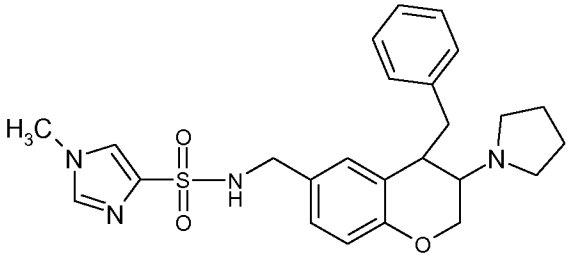
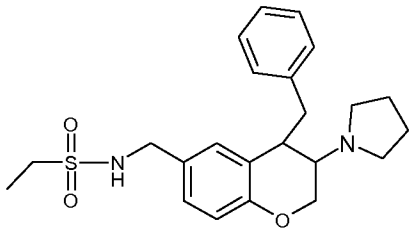
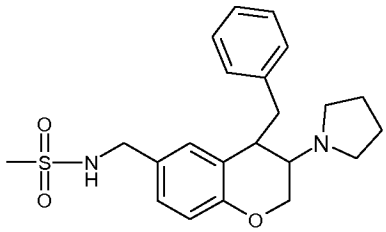
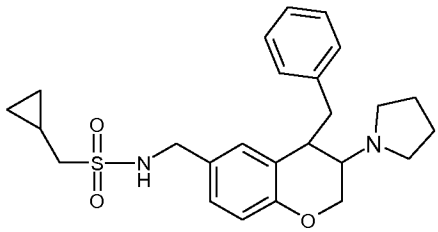
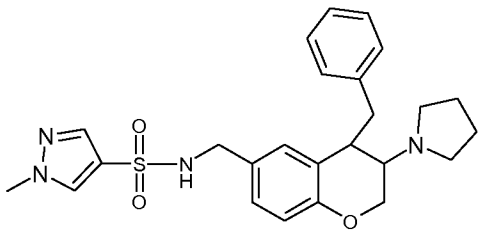
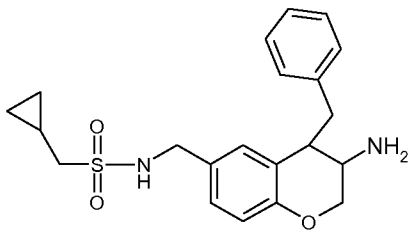
29		cis-Ethanesulfonic acid [2-(-4-benzyl-7-fluoro-3-methylamino-chroman-6-yloxy)-ethyl]-amide
30		trans-Ethanesulfonic acid [2-(-4-benzyl-7-fluoro-3-methylamino-chroman-6-yloxy)-ethyl]-amide
31		cis-1-Methyl-1H-imidazole-4-sulfonic acid (-4-benzyl-7-fluoro-3-methylamino-chroman-6-ylmethyl)-amide
32		trans-1-Methyl-1H-imidazole-4-sulfonic acid (-4-benzyl-7-fluoro-3-methylamino-chroman-6-ylmethyl)-amide
33		cis-N-((-4-benzyl-3-((2-cyclopropylethyl)amino)chroman-6-yl)methyl)-1-methyl-1H-imidazole-4-sulfonamide 2,2,2-trifluoroacetate
34		cis-N-((-4-benzyl-3-((2-cyclopentylethyl)amino)chroman-6-yl)methyl)-1-methyl-1H-imidazole-4-sulfonamide 2,2,2-trifluoroacetate
35		cis-N-((-4-benzyl-3-(propylamino)chroman-6-yl)methyl)-1-methyl-1H-imidazole-4-sulfonamide 2,2,2-trifluoroacetate

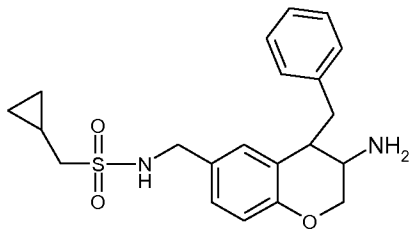
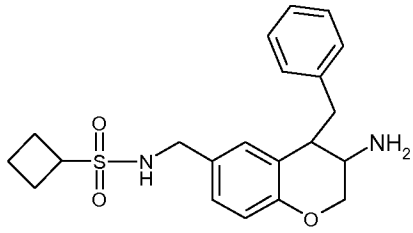
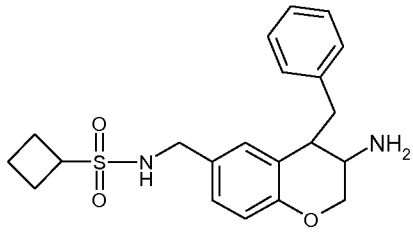
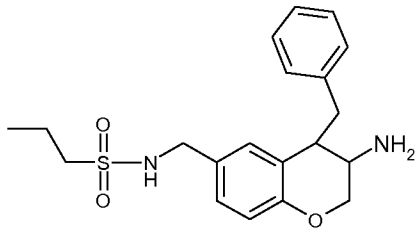
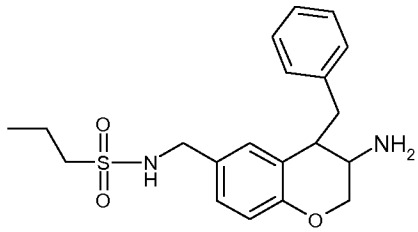
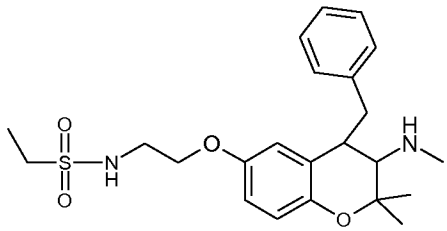
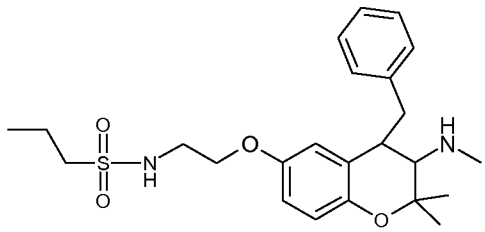
36		cis-N-((-4-benzyl-3-(neopentylamino)chroman-6-yl)methyl)-1-methyl-1H-imidazole-4-sulfonamide 2,2,2-trifluoroacetate
37		cis-N-((-4-benzyl-3-(isobutylamino)chroman-6-yl)methyl)-1-methyl-1H-imidazole-4-sulfonamide 2,2,2-trifluoroacetate
38		cis-N-((-4-benzyl-3-((cyclopropylmethyl)amino)chroman-6-yl)methyl)-1-methyl-1H-imidazole-4-sulfonamide 2,2,2-trifluoroacetate
39		cis-N-((-4-benzyl-3-(isopentylamino)chroman-6-yl)methyl)-1-methyl-1H-imidazole-4-sulfonamide 2,2,2-trifluoroacetate
40		cis-N-((-4-benzyl-3-((cyclopentylmethyl)amino)chroman-6-yl)methyl)-1-methyl-1H-imidazole-4-sulfonamide 2,2,2-trifluoroacetate
41		cis-N-((-4-benzyl-3-((cyclobutylmethyl)amino)chroman-6-yl)methyl)-1-methyl-1H-imidazole-4-sulfonamide 2,2,2-trifluoroacetate

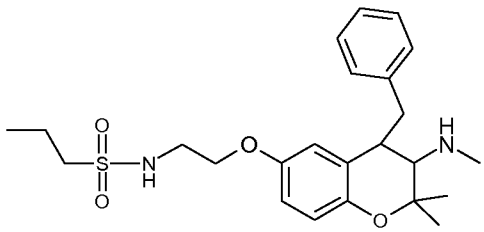
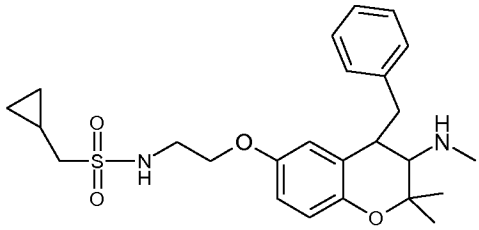
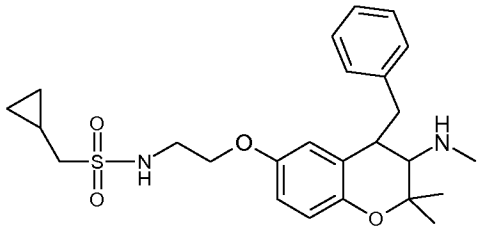
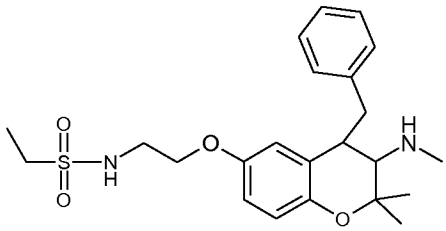
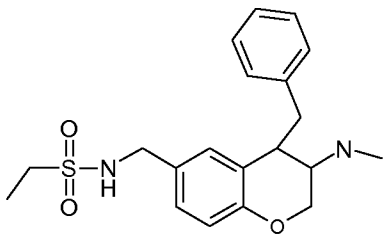
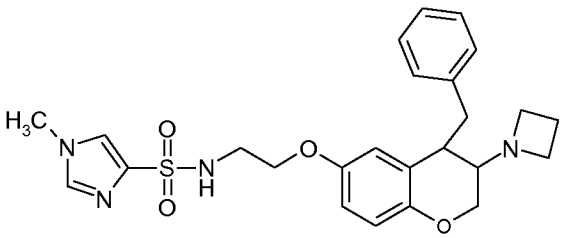
42		Thiophene-2-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide 2,2,2-trifluoroacetate
43		3-Methyl-piperidine-1-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide 2,2,2-trifluoroacetate
44		Morpholine-4-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide 2,2,2-trifluoroacetate
45		1,3-Dimethyl-1H-pyrazole-4-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide 2,2,2-trifluoroacetate
46		1-Methyl-1H-pyrazole-3-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide 2,2,2-trifluoroacetate
47		Butane-2-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide 2,2,2-trifluoroacetate
48		Propane-2-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide 2,2,2-trifluoroacetate

49		Thiophene-3-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide 2,2,2-trifluoroacetate
50		2,5-Dimethyl-furan-3-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide 2,2,2-trifluoroacetate
51		2-Methyl-propane-1-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide 2,2,2-trifluoroacetate
52		5-Methyl-furan-2-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide 2,2,2-trifluoroacetate
53		5-Methyl-thiophene-2-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide 2,2,2-trifluoroacetate
54		Furan-3-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide 2,2,2-trifluoroacetate
55		2,5-Dimethyl-2H-pyrazole-3-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide 2,2,2-trifluoroacetate

		
56		4-Methyl-thiophene-2-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide 2,2,2-trifluoroacetate
57		1-Ethyl-1H-pyrazole-4-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide 2,2,2-trifluoroacetate
58		2,3-Dimethyl-3H-imidazole-4-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide 2,2,2-trifluoroacetate
59		1,5-Dimethyl-1H-pyrazole-4-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide 2,2,2-trifluoroacetate
60		cis-N-(-4-Benzyl-3-methylamino-chroman-6-ylmethyl)-methanesulfonamide
61		trans-N-(-4-Benzyl-3-methylamino-chroman-6-ylmethyl)-methanesulfonamide

62		cis-1-Methyl-1H-imidazole-4-sulfonic acid (-4-benzyl-3-pyrrolidin-1-yl-chroman-6-ylmethyl)-amide
63		cis-Ethanesulfonic acid (-4-benzyl-3-pyrrolidin-1-yl-chroman-6-ylmethyl)-amide
64		cis-N-(-4-Benzyl-3-pyrrolidin-1-yl-chroman-6-ylmethyl)-methanesulfonamide
65		cis-N-(-4-Benzyl-3-pyrrolidin-1-yl-chroman-6-ylmethyl)-C-cyclopropyl-methanesulfonamide
66		cis-1-Methyl-1H-pyrazole-4-sulfonic acid (-4-benzyl-3-pyrrolidin-1-yl-chroman-6-ylmethyl)-amide
67		cis-N-(-3-Amino-4-benzyl-chroman-6-ylmethyl)-C-cyclopropyl-methanesulfonamide

68		trans-N-(-3-Amino-4-benzyl-chroman-6-ylmethyl)-C-cyclopropyl-methanesulfonamide
69		cis-Cyclobutanesulfonic acid (-3-amino-4-benzyl-chroman-6-ylmethyl)-amide
70		trans-Cyclobutanesulfonic acid (-3-amino-4-benzyl-chroman-6-ylmethyl)-amide
71		cis-Propane-1-sulfonic acid (-3-amino-4-benzyl-chroman-6-ylmethyl)-amide
72		trans-Propane-1-sulfonic acid (-3-amino-4-benzyl-chroman-6-ylmethyl)-amide
73		trans-Ethanesulfonic acid [2-(-4-benzyl-2,2-dimethyl-3-methylamino-chroman-6-yloxy)-ethyl]-amide
74		cis-Propane-1-sulfonic acid [2-(-4-benzyl-2,2-dimethyl-3-methylamino-chroman-6-yloxy)-ethyl]-amide

75		trans-Propane-1-sulfonic acid [2-(-4-benzyl-2,2-dimethyl-3-methylamino-chroman-6-yloxy)-ethyl]-amide
76		cis-N-[2-(-4-Benzyl-2,2-dimethyl-3-methylamino-chroman-6-yloxy)-ethyl]-C-cyclopropyl-methanesulfonamide
77		trans-N-[2-(-4-Benzyl-2,2-dimethyl-3-methylamino-chroman-6-yloxy)-ethyl]-C-cyclopropyl-methanesulfonamide
78		cis-Ethanesulfonic acid [2-(-4-benzyl-2,2-dimethyl-3-methylamino-chroman-6-yloxy)-ethyl]-amide
79		cis-N-{[4-Benzyl-3-(methyl-amino)-3,4-dihydro-2H-chromen-6-yl]methyl}ethane-sulfonamide. (Isomer 2)
80		cis-1-Methyl-1H-imidazole-4-sulfonic acid [2-(3-azetidin-1-yl-4-benzyl-chroman-6-yloxy)-ethyl]-amide. (Isomer 2)

Biological testing

1. [^{3}H]-Glycine uptake into recombinant CHO cells expressing human GlyT1:

Human GlyT1c expressing recombinant hGlyT1c_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 [^{3}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. IC_{50} calculations were made by four-parametric logistic nonlinear regression analysis (GraphPad Prism) using determinations within the range of linear increase of [^{3}H]-glycine incorporation between 60 and 120 min.

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

Radioligand binding to human GlyT1c 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 1:

	radioligand binding
Example	K_{iapp} [µM]
1a	≤ 0.01
1b	≤ 0.01
2a	≤ 0.01
2b	≤ 0.01
3a	≤ 0.1
3b	≤ 1.0
4a	≤ 0.01
4b	≤ 0.1
5a	≤ 0.01
5b	≤ 0.01
6a	≤ 0.01
6b	≤ 0.01
7a	≤ 0.01
7b	≤ 0.1
8a	≤ 0.01
8b	≤ 0.1

9a	≤ 0.1
9b	≤ 1.0
10	≤ 0.01
11	≤ 1.0
12	≤ 0.01
13	≤ 0.01
14	≤ 0.1
15	≤ 0.01
16	≤ 0.01
17	≤ 0.01
18	≤ 0.1
19	≤ 1.0
20	≤ 0.1
21	≤ 0.1
22	≤ 0.01
23	≤ 0.1
24	≤ 0.1
25	≤ 0.1
26	≤ 1.0
27	≤ 0.01
28	≤ 0.1
29	≤ 0.1
30	≤ 1.0
31	≤ 0.1
32	≤ 0.01
33	≤ 0.01
34	≤ 10
35	≤ 0.01
36	≤ 0.1
37	≤ 0.01
39	≤ 0.01
40	≤ 0.1
41	≤ 0.01
43	≤ 1.0
44	≤ 10
45	≤ 1.0
46	≤ 1.0
47	≤ 0.1
48	≤ 1.0

49	≤ 1.0
50	≤ 0.1
51	≤ 1.0
52	≤ 1.0
53	≤ 1.0
54	≤ 0.1
55	≤ 10
56	≤ 0.1
57	≤ 1.0
58	≤ 1.0
59	≤ 1.0
60	≤ 1.0
61	≤ 1.0
62	≤ 0.01
63	≤ 0.1
64	≤ 1.0
65	≤ 0.01
66	≤ 0.01
67	≤ 0.01
68	≤ 0.1
69	≤ 0.1
70	≤ 1.0
71	≤ 0.1
72	≤ 0.1
73	≤ 1.0
74	≤ 1.0
75	≤ 1.0
76	≤ 1.0
77	≤ 1.0
79	≤ 0.1
80	≤ 0.01

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

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.

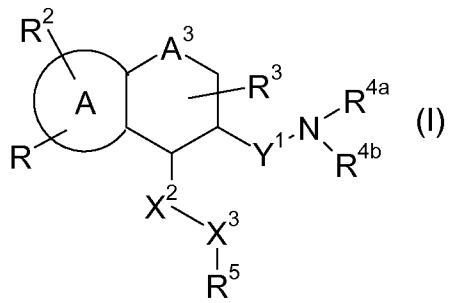
Compounds were added at 1 µM in HBSS-pH 7.4 (hanks balanced salt solution) to either the apical or basolateral side of MDR1-MDCK cell monolayers grown on Millicell 96-Cell polycarbonate filters. Samples were collected from both apical and basolateral sides at time 0 and after 1h incubation at 37C, compounds 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.

Table 2:

Example	Efflux ratio
25	1.4

We claim:

1. Compounds of the formula (I)



(I)

wherein

A is a 5- or 6-membered ring;

R is R^1-W-A^1-Q-Y-A^2-X^1-;

R^1 is hydrogen, C_1-C_6-alkyl, C_3-C_{12}-cycloalkyl-C_1-C_4-alkyl, halogenated C_1-C_6-alkyl, tri-(C_1-C_4-alkyl)-silyl-C_1-C_4-alkyl, hydroxy-C_1-C_4-alkyl, C_1-C_6-alkoxy-C_1-C_4-alkyl, amino-C_1-C_4-alkyl, C_1-C_6-alkylamino-C_1-C_4-alkyl, di-C_1-C_6-alkylamino-C_1-C_4-alkyl, C_1-C_6-alkylcarbonylamino-C_1-C_4-alkyl, C_1-C_6-alkyloxycarbonylamino-C_1-C_4-alkyl, C_1-C_6-alkylaminocarbonylamino-C_1-C_4-alkyl, di-C_1-C_6-alkylaminocarbonylamino-C_1-C_4-alkyl, C_1-C_6-alkylsulfonylamino-C_1-C_4-alkyl, (optionally substituted C_6-C_{12}-aryl-C_1-C_6-alkyl)amino-C_1-C_4-alkyl, optionally substituted C_6-C_{12}-aryl-C_1-C_4-alkyl, optionally substituted C_3-C_{12}-heterocyclyl-C_1-C_4-alkyl, C_3-C_{12}-cycloalkyl, C_1-C_6-alkylcarbonyl, C_1-C_6-alkoxycarbonyl, halogenated C_1-C_6-alkoxycarbonyl, C_6-C_{12}-aryloxycarbonyl, aminocarbonyl, C_1-C_6-alkylaminocarbonyl, (halogenated C_1-C_4-alkyl)aminocarbonyl, C_6-C_{12}-arylaminocarbonyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, optionally substituted C_6-C_{12}-aryl, hydroxy, C_1-C_6-alkoxy, halogenated C_1-C_6-alkoxy, C_1-C_6-hydroxyalkoxy, C_1-C_6-alkoxy-C_1-C_4-alkoxy, amino-C_1-C_4-alkoxy, C_1-C_6-alkylamino-C_1-C_4-alkoxy, di-C_1-C_6-alkylamino-C_1-C_4-alkoxy, C_1-C_6-alkylcarbonylamino-C_1-C_4-alkoxy, C_6-C_{12}-arylcarbonylamino-C_1-C_4-alkoxy, C_1-C_6-alkoxycarbonylamino-C_1-C_4-alkoxy, C_6-C_{12}-aryl-C_1-C_4-alkoxy, C_1-C_6-alkylsulfonylamino-C_1-C_4-alkoxy, (halogenated C_1-C_6-alkyl)sulfonylamino-C_1-C_4-alkoxy, C_6-C_{12}-arylsulfonylamino-C_1-C_4-alkoxy, (C_6-C_{12}-aryl-C_1-C_6-alkyl)sulfonylamino-C_1-C_4-alkoxy, C_3-C_{12}-heterocyclylsulfonylamino-C_1-C_4-alkoxy, C_3-C_{12}-heterocyclyl-C_1-C_4-alkoxy, C_6-C_{12}-aryloxy, C_3-C_{12}-heterocyclyloxy, C_1-C_6-alkylthio, halogenated C_1-C_6-alkylthio, C_1-C_6-alkylamino, (halogenated C_1-C_6-alkyl)amino, di-C_1-C_6-alkylamino, di-

(halogenated C_1-C_6-alkyl)amino, C_1-C_6-alkylcarbonylamino, (halogenated C_1-C_6-alkyl)carbonylamino, C_6-C_{12}-arylcarbonylamino, C_1-C_6-alkylsulfonylamino, (halogenated C_1-C_6-alkyl)sulfonylamino, C_6-C_{12}-arylsulfonylamino or optionally substituted C_3-C_{12}-heterocyclyl;

W is $-NR^8-$ or a bond;

A^1 is optionally substituted C_1-C_4-alkylene or a bond;

Q is $-S(O)_2-$ or $-C(O)-$;

Y is $-NR^9-$ or a bond;

A^2 is optionally substituted C_1-C_4-alkylene, C_1-C_4-alkylene-CO-, -CO-C_1-C_4-alkylene, C_1-C_4-alkylene-O-C_1-C_4-alkylene, C_1-C_4-alkylene-NR^{10}-C_1-C_4-alkylene, optionally substituted C_2-C_4-alkenylen, optionally substituted C_2-C_4-alkynylene, optionally substituted C_6-C_{12}-arylene, optionally substituted C_6-C_{12}-heteroarylene or a bond;

X^1 is -O-, $-NR^{11}-$, -S-, optionally substituted C_1-C_4-alkylene, optionally substituted C_2-C_4-alkenylen, optionally substituted C_2-C_4-alkynylene;

R^2 is hydrogen, halogen, C_1-C_6-alkyl, halogenated C_1-C_4-alkyl, hydroxy-C_1-C_4-alkyl, -CN, C_2-C_6-alkenyl, C_2-C_6-alkynyl, optionally substituted C_6-C_{12}-aryl, hydroxy, C_1-C_6-alkoxy, halogenated C_1-C_6-alkoxy, C_1-C_6-alkoxycarbonyl, C_2-C_6-alkenyloxy, C_6-C_{12}-aryl-C_1-C_4-alkoxy, C_1-C_6-alkylcarbonyloxy, C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl, aminosulfonyl, amino, C_1-C_6-alkylamino, C_2-C_6-alkenylamino, nitro or optionally substituted C_3-C_{12}-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^3 is -O-, -S- or $-NR^{16}-$;

R^3 is hydrogen, halogen, C_1-C_6-alkyl or C_1-C_6-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 C_1-C_4-alkylene;

R^{4a} is hydrogen, C_1-C_6-alkyl, C_3-C_{12}-cycloalkyl-C_1-C_4-alkyl, halogenated C_1-C_4-alkyl, hydroxy-C_1-C_4-alkyl, C_1-C_6-alkoxy-C_1-C_4-alkyl, amino-C_1-C_4-alkyl, CH_2CN, C_6-C_{12}-aryl-C_1-C_4-alkyl, C_3-C_{12}-cycloalkyl, -CHO, C_1-C_4-alkylcarbonyl,

(halogenated C_1-C_4-alkyl)carbonyl, C_6-C_{12}-arylcarbonyl, C_1-C_4-alkoxycarbonyl, C_6-C_{12}-aryloxycarbonyl, C_1-C_6-alkylaminocarbonyl, C_2-C_6-alkenyl, -C(=NH)NH_2, -C(=NH)NHCN, C_1-C_6-alkylsulfonyl, C_6-C_{12}-arylsulfonyl, amino, -NO or C_3-C_{12}-heterocyclyl; or

R^{4a} is optionally substituted C_1-C_4-alkylene that is bound to a carbon atom in Y^1;

R^{4b} is hydrogen, C_1-C_6-alkyl, halogenated C_1-C_4-alkyl, hydroxy-C_1-C_4-alkyl, C_1-C_6-alkoxy-C_1-C_4-alkyl, amino-C_1-C_4-alkyl, CH_2CN, -CHO, C_1-C_4-alkylcarbonyl, (halogenated C_1-C_4-alkyl)carbonyl, C_6-C_{12}-arylcarbonyl, C_1-C_4-alkoxycarbonyl, C_6-C_{12}-aryloxycarbonyl, C_1-C_6-alkylaminocarbonyl, C_2-C_6-alkenyl, -C(=NH)NH_2, -C(=NH)NHCN, C_1-C_6-alkylsulfonyl, C_6-C_{12}-arylsulfonyl, amino, -NO or C_3-C_{12}-heterocyclyl; or

R^{4a}, R^{4b}
together are optionally substituted C_1-C_6-alkylene, wherein one -CH_2- of C_1-C_4-alkylene may be replaced by an oxygen atom or -NR^{17};

X^2 is -O-, -NR^6-, -S-, >$CR^{12a}R^{12b}$ or a bond;

X^3 is -O-, -NR^7-, -S-, >$CR^{13a}R^{13b}$ or a bond;

R^5 is optionally substituted C_6-C_{12}-aryl, optionally substituted C_3-C_{12}-cycloalkyl or optionally substituted C_3-C_{12}-heterocyclyl;

R^6 is hydrogen or C_1-C_6-alkyl;

R^7 is hydrogen or C_1-C_6-alkyl;

R^8 is hydrogen or C_1-C_6-alkyl;

R^9 is hydrogen, C_1-C_6-alkyl, C_3-C_{12}-cycloalkyl, amino-C_1-C_6-alkyl, optionally substituted C_6-C_{12}-aryl-C_1-C_4-alkyl or C_3-C_{12}-heterocyclyl; or

R^9, R^1
together are C_1-C_4-alkylene; or

R^9 is C_1-C_4-alkylene that is bound to a carbon atom in A^2 and A^2 is C_1-C_4-alkylene or to a carbon atom in X^1 and X^1 is C_1-C_4-alkylene;

R^{10} is hydrogen, C_1-C_6-alkyl or C_1-C_6-alkylsulfonyl;

R^{11} is hydrogen or C_1-C_6-alkyl, or

R^9, R^{11}
together are C_1-C_4-alkylene,

R^{12a} is hydrogen, optionally substituted C_1-C_6-alkyl, C_1-C_6-alkylamino-C_1-C_4-alkyl, di-C_1-C_6-alkylamino-C_1-C_4-alkyl, C_3-C_{12}-heterocyclyl-C_1-C_6-alkyl, optionally substituted C_6-C_{12}-aryl or hydroxy;

R^{12b} is hydrogen or C_1-C_6-alkyl, or

R^{12a}, R^{12b}
together are carbonyl or optionally substituted C_1-C_4-alkylene, wherein one -CH_2- of C_1-C_4-alkylene may be replaced by an oxygen atom or -NR^{14}-;

R^{13a} is hydrogen, optionally substituted C_1-C_6-alkyl, C_1-C_6-alkylamino-C_1-C_4-alkyl, di-C_1-C_6-alkylamino-C_1-C_4-alkyl, C_3-C_{12}-heterocyclyl-C_1-C_6-alkyl, optionally substituted C_6-C_{12}-aryl or hydroxy;

R^{13b} is hydrogen or C_1-C_6-alkyl, or

R^{13a}, R^{13b}
together are carbonyl or optionally substituted C_1-C_4-alkylene, wherein one -CH_2- of C_1-C_4-alkylene may be replaced by an oxygen atom or -NR^{15}-;

R^{14} is hydrogen or C_1-C_6-alkyl;

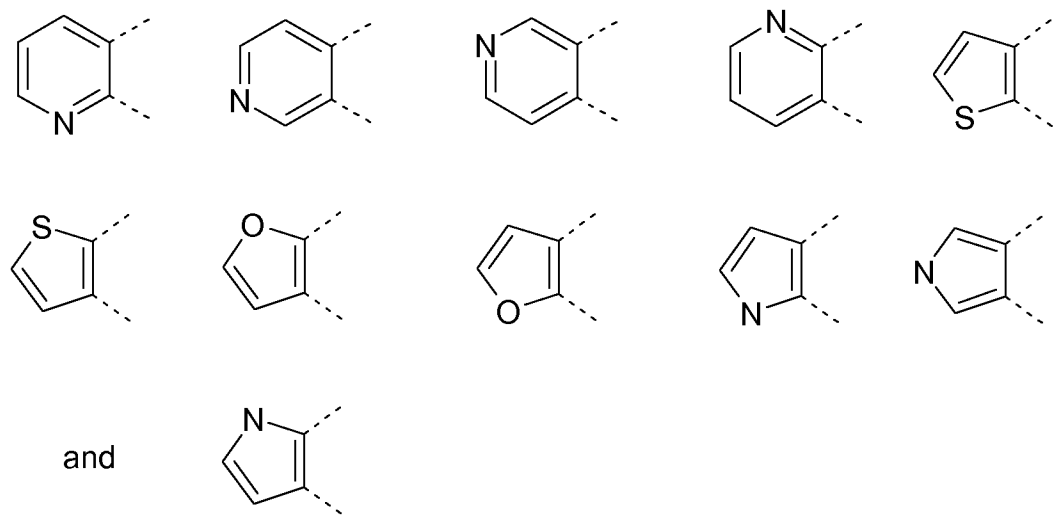
R^{15} is hydrogen or C_1-C_6-alkyl;

R^{16} is hydrogen, C_1-C_6-alkyl, C_3-C_{12}-cycloalkyl-C_1-C_4-alkyl, halogenated C_1-C_4-alkyl, hydroxy-C_1-C_4-alkyl, C_1-C_6-alkoxy-C_1-C_4-alkyl, amino-C_1-C_4-alkyl, CH_2CN, C_6-C_{12}-aryl-C_1-C_4-alkyl, C_3-C_{12}-cycloalkyl, -CHO, C_1-C_4-alkylcarbonyl, (halogenated C_1-C_4-alkyl)carbonyl, C_6-C_{12}-arylcarbonyl, C_1-C_4-alkoxycarbonyl, C_6-C_{12}-aryloxycarbonyl, C_1-C_6-alkylaminocarbonyl, C_2-C_6-alkenyl, -C(=NH)NH_2, -C(=NH)NHCN, C_1-C_6-alkylsulfonyl, C_6-C_{12}-arylsulfonyl, amino, -NO or C_3-C_{12}-heterocyclyl; and

R^{17} is hydrogen or C_1-C_6-alkyl,

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:



and

..

3. Compound as claimed in claim 1 or 2, wherein -Y-A^2-X^1- comprises at least 2, 3 or 4 atoms in the main chain.

4. Compound as claimed in any one of claims 1 to 3, wherein R^1 is C_1-C_6-alkyl, C_3-C_{12}-cycloalkyl-C_1-C_4-alkyl, C_3-C_{12}-cycloalkyl, or optionally substituted C_3-C_{12}-heterocyclyl.

5. Compound as claimed in any one of claims 1 to 4, wherein A^1 is a bond.

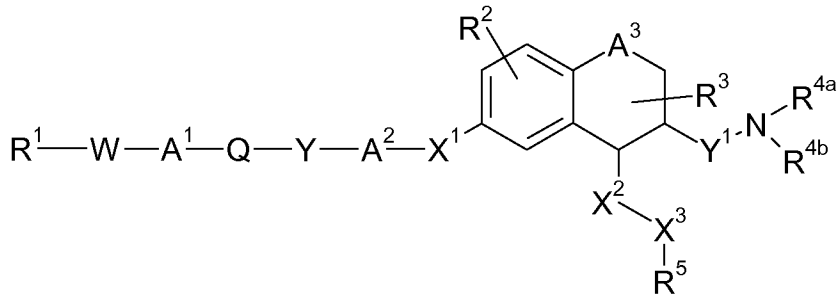
6. Compound as claimed in any one of claims 1 to 5, wherein W is a bond and Y is a bond.

7. Compound as claimed in any one of claims 1 to 5, wherein W is a bond and Y is –NR^9-.

8. Compound as claimed in any one of claims 1 to 7, wherein X^1 is -O- and A^2 is C_1-C_4-alkylene, or X^1 is C_1-C_4-alkylene and A^2 is a bond.

9. Compound as claimed in any one of claims 1 to 8, wherein R^1-W-A^1-Q-Y-A^2-X^1- is R^1-$S(O)_2$-NR^9-A^2-X^1- or R^1-$S(O)_2$-X^1-.

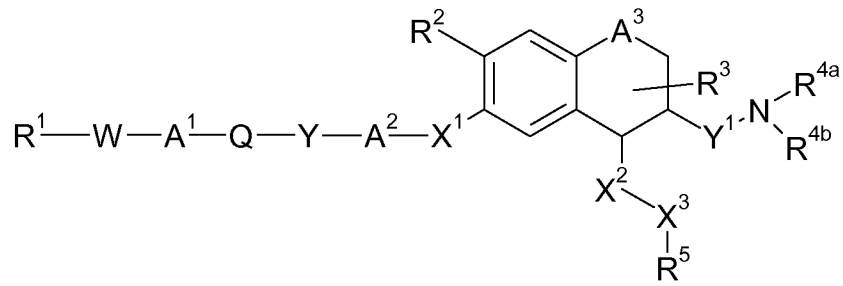
10. Compound as claimed in any one of claims 1 to 9, having the formula

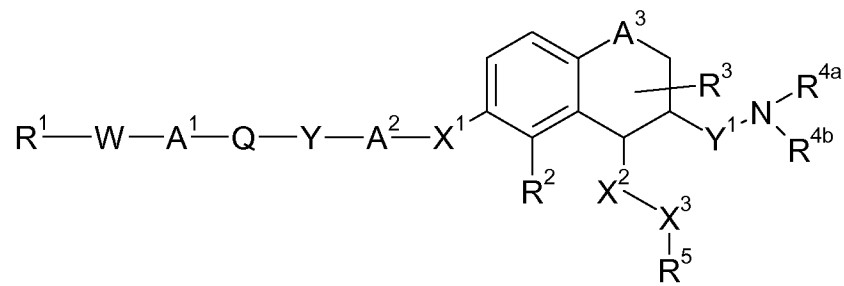


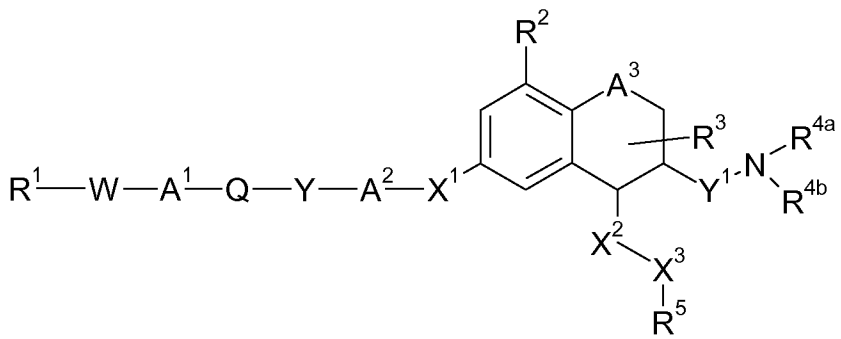
wherein R^1, W, A^1, Q, Y, A^2, X^1, R^2, A^3, R^3, Y^1, R^{4a}, R^{4b}, X^2, X^3, R^5 are as defined in any one of claims 1 to 9.

11. Compound as claimed in any one of claims 1 to 10, wherein R^2 is hydrogen or halogen.

12. Compound as claimed in claim 10 or 11, having one of the formulae





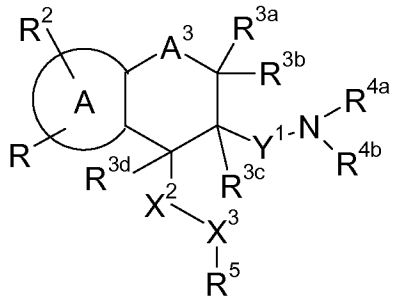


wherein R^1, W, A^1, Q, Y, A^2, X^1, R^2, A^3, R^3, Y^1, R^{4a}, R^{4b}, X^2, X^3, R^5 are as defined in any of claims 1 to 11.

13. Compound as claimed in any one of claims 1 to 12, wherein A^3 is -O-.

14. Compound as claimed in any one of claims 1 to 13, wherein R^3 is hydrogen or C_1-C_6-alkyl.

15. Compound as claimed in any one of claims 1 to 14, having the formula



wherein R^{3a}, R^{3b}, R^{3c}, R^{3d} independently have the meaning of R^3, and A, R, R^2, A^3, R^3, Y^1, R^{4a}, R^{4b}, X^2, X^3, R^5 are as defined in any one of claims 1 to 14.

16. Compound as claimed in claim 1 to 14, wherein Y^1 is a bond.

17. Compound as claimed in claim 1 to 16, wherein R^{4a} is hydrogen or C_1-C_6-alkylC_3-C_{12}-cycloalkyl, C_3-C_{12}-cycloalkyl-C_1-C_4-alkyl, or C_3-C_{12}-heterocyclyl.

18. Compound as claimed in any one of claims 1 to 17, wherein R^{4b} is hydrogen or C_1-C_6-alkyl.

19. Compound as claimed in any one of claims 1 to 16, wherein R^{4a}, R^{4b} together are optionally substituted C_1-C_6-alkylene, wherein one -CH_2- of C_1-C_4-alkylene may be replaced by an oxygen atom.

20. Compound as claimed in any one of claims 1 to 19, wherein X^2 is $CR^{12a}R^{12b}$.

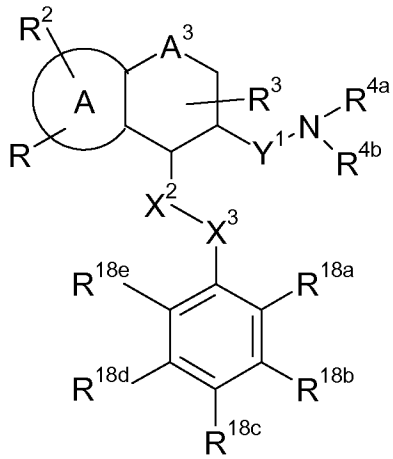
21. Compound as claimed in any one of claims 1 to 20, wherein X^3 is a bond.

22. Compound as claimed in any one of claims 1 to 21, wherein R^{12a} is hydrogen or C_1-C_6-alkyl and R^{12b} is hydrogen or C_1-C_6-alkyl.

23. Compound as claimed in any one of claims 1 to 21, wherein R^{12a}, R^{12b} together are optionally substituted C_1-C_4-alkylene.

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, R^2, A^3, R^3, Y^1, R^{4a}, R^{4b}, X^2, X^3 are as defined in any one of claims 1 to 23; and
R^{18a}, R^{18b}, R^{18c}, R^{18d}, R^{18e}
independently are hydrogen, halogen, or halogenated C_1-C_6-alkyl.

26. Compound as claimed in any one of claims 1 to 25, wherein R^9 is hydrogen; or R^9 is C_1-C_4-alkylene that is bound to a carbon atom in X^1 and X^1 is C_1-C_4-alkylene.

27. Compound as claimed in claim 1, wherein

A is a benzene ring;

R is R^1-W-A^1-Q-Y-A^2-X^1-;

R^1 is C_1-C_6-alkyl, C_3-C_{12}-cycloalkyl-C_1-C_4-alkyl, C_3-C_{12}-cycloalkyl, or optionally substituted C_3-C_{12}-heterocyclyl;

W is a bond;

A^1 is a bond;

Q is $-S(O)_2-$;

Y is $-NR^9-$ or a bond;

A^2 is C_1-C_4-alkylene or a bond;

X^1 is -O- or C_1-C_4-alkylene;

R^2 is hydrogen or halogen;

A^3 is -O-;

R^3 is hydrogen or C_1-C_6-alkyl;

Y^1 is a bond;

R^{4a} is hydrogen, C_1-C_6-alkyl, C_3-C_{12}-cycloalkyl, or C_3-C_{12}-cycloalkyl-C_1-C_4-alkyl; or

R^{4b} is hydrogen; or

R^{4a}, R^{4b}
together are C_1-C_6-alkylene;

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

X^3 is a bond;

R^5 is optionally substituted phenyl;

R^9 is hydrogen; or

R^9 is C_1-C_4-alkylene that is bound to a carbon atom in X^1 and X^1 is C_1-C_4-alkylene;

R^{12a} is hydrogen or C_1-C_6-alkyl; and

R^{12b} is hydrogen; or

R^{12a}, R^{12b}
together are C_1-C_4-alkylene.

28. The compound as claimed in claim 1 which is:.
cis-N-(2-{[-4-Benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]oxy}ethyl)-1-methyl-1H-pyrazole-4-sulfonamide;
trans-N-(2-{[-4-Benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]oxy}ethyl)-1-methyl-1H-pyrazole-4-sulfonamide;
cis-N-(2-{[-4-Benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]oxy}ethyl)-1-methyl-1H-imidazole-4-sulfonamide;

trans-N-(2-{[-4-Benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]oxy}ethyl)-1-methyl-1H-imidazole-4-sulfonamide;
cis-N-(2-{[-4-Benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]oxy}ethyl)propane-1-sulfonamide;
trans-N-(2-{[-4-Benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]oxy}ethyl)propane-1-sulfonamide;
cis-N-(2-{[-4-Benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]oxy}ethyl)-1-cyclopropylmethanesulfonamide;
trans-N-(2-{[-4-Benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]oxy}ethyl)-1-cyclopropylmethanesulfonamide;
cis-1-Methyl-1H-imidazole-4-sulfonic acid (4-benzyl-3-methylamino-chroman-6-ylmethyl)-amide;
trans-1-Methyl-1H-imidazole-4-sulfonic acid (4-benzyl-3-methylamino-chroman-6-ylmethyl)-amide;
cis-N-{[4-Benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]methyl}-1-methyl-1H-pyrazole-4-sulfonamide;
trans-N-{[-4-Benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]methyl}-1-methyl-1H-pyrazole-4-sulfonamide;
cis-N-{[4-Benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]methyl}propane-1-sulfonamide (a) and *trans*-N-{[4-benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]methyl}propane-1-sulfonamide;
cis-N-{[4-Benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]methyl}-1-cyclopropylmethanesulfonamide;
trans-N-{[4-Benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]methyl}-1-cyclopropylmethanesulfonamide;
cis-N-{[4-Benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]methyl}ethanesulfonamide;
trans-N-{[4-benzyl-3-(methylamino)-3,4-dihydro-2H-chromen-6-yl]methyl}ethanesulfonamide;
1-Methyl-1H-imidazole-4-sulfonic acid [2-((3S,4S)-3-azetidin-1-yl-4-benzyl-chroman-6-yloxy)-ethyl]-amide;
N-[2-((3S,4S)-3-Azetidin-1-yl-4-benzyl-chroman-6-yloxy)-ethyl]-C-cyclopropyl-methanesulfonamide;
1-Methyl-1H-imidazole-4-sulfonic acid ((3S,4S)-3-amino-4-benzyl-chroman-6-ylmethyl)-amide;
1-Methyl-1H-imidazole-4-sulfonic acid ((3R,4S)-3-amino-4-benzyl-chroman-6-ylmethyl)-amide;
Propane-1-sulfonic acid [2-((3S,4S)-3-azetidin-1-yl-4-benzyl-chroman-6-yloxy)-ethyl]-amide;
1-Methyl-1H-pyrazole-4-sulfonic acid ((3R,4R)-3-azetidin-1-yl-4-benzyl-chroman-6-ylmethyl)-amide;

1-Methyl-1H-pyrazole-4-sulfonic acid [2-((3S,4S)-3-azetidin-1-yl-4-benzyl-chroman-6-yloxy)-ethyl]-amide;
1-Methyl-1H-imidazole-4-sulfonic acid ((3R,4R)-3-azetidin-1-yl-4-benzyl-chroman-6-ylmethyl)-amide;
Ethanesulfonic acid [2-((3S,4S)-3-azetidin-1-yl-4-benzyl-chroman-6-yloxy)-ethyl]-amide;
Ethanesulfonic acid (3-azetidin-1-yl-4-benzyl-chroman-6-ylmethyl)-amide;
Propane-1-sulfonic acid (3-azetidin-1-yl-4-benzyl-chroman-6-ylmethyl)-amide;
N-(3-Azetidin-1-yl-4-benzyl-chroman-6-ylmethyl)-C-cyclopropyl-methane-sulfonamide;
1-Methyl-1H-imidazole-4-sulfonic acid [(3S,4S)-4-benzyl-3-(cyclohexylmethyl-amino)-chroman-6-lmethyl]-amide;
Ethanesulfonic acid ((3R,4R)-3-amino-4-benzyl-chroman-6-ylmethyl)-amide;
Ethanesulfonic acid ((3S,4R)-3-amino-4-benzyl-chroman-6-ylmethyl)-amide;
Cyclobutanesulfonic acid ((3R,4R)-4-benzyl-3-methylamino-chroman-6-ylmethyl)-amide;
Cyclobutanesulfonic acid ((3S,4R)-4-benzyl-3-methylamino-chroman-6-ylmethyl)-amide;
cis-Ethanesulfonic acid (-4-benzyl-7-fluoro-3-methylamino-chroman-6-ylmethyl)-amide;
trans-Ethanesulfonic acid (-4-benzyl-7-fluoro-3-methylamino-chroman-6-ylmethyl)-amide;
cis-Ethanesulfonic acid [2-(-4-benzyl-7-fluoro-3-methylamino-chroman-6-yloxy)-ethyl]-amide;
trans-Ethanesulfonic acid [2-(-4-benzyl-7-fluoro-3-methylamino-chroman-6-yloxy)-ethyl]-amide;
cis-1-Methyl-1H-imidazole-4-sulfonic acid (-4-benzyl-7-fluoro-3-methylamino-chroman-6-ylmethyl)-amide;
trans-1-Methyl-1H-imidazole-4-sulfonic acid (-4-benzyl-7-fluoro-3-methylamino-chroman-6-ylmethyl)-amide;
cis-N-((-4-benzyl-3-((2-cyclopropylethyl)amino)chroman-6-yl)methyl)-1-methyl-1H-imidazole-4-sulfonamide;
cis-N-((-4-benzyl-3-((2-cyclopentylethyl)amino)chroman-6-yl)methyl)-1-methyl-1H-imidazole-4-sulfonamide;
cis-N-((-4-benzyl-3-(propylamino)chroman-6-yl)methyl)-1-methyl-1H-imidazole-4-sulfonamide;
cis-N-((-4-benzyl-3-(neopentylamino)chroman-6-yl)methyl)-1-methyl-1H-imidazole-4-sulfonamide;

cis-N-((-4-benzyl-3-(isobutylamino)chroman-6-yl)methyl)-1-methyl-1H-imidazole-4-sulfonamide;
cis-N-((-4-benzyl-3-((cyclopropylmethyl)amino)chroman-6-yl)methyl)-1-methyl-1H-imidazole-4-sulfonamide;
cis-N-((-4-benzyl-3-(isopentylamino)chroman-6-yl)methyl)-1-methyl-1H-imidazole-4-sulfonamide;
cis-N-((-4-benzyl-3-((cyclopentylmethyl)amino)chroman-6-yl)methyl)-1-methyl-1H-imidazole-4-sulfonamide;
cis-N-((-4-benzyl-3-((cyclobutylmethyl)amino)chroman-6-yl)methyl)-1-methyl-1H-imidazole-4-sulfonamide;
Thiophene-2-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide;
3-Methyl-piperidine-1-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide;
Morpholine-4-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide;
1,3-Dimethyl-1H-pyrazole-4-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide;
1-Methyl-1H-pyrazole-3-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide;
Butane-2-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide;
Propane-2-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide;
Thiophene-3-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide;
2,5-Dimethyl-furan-3-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide;
2-Methyl-propane-1-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide;
5-Methyl-furan-2-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide;
5-Methyl-thiophene-2-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide;
Furan-3-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide;
2,5-Dimethyl-2H-pyrazole-3-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide;
4-Methyl-thiophene-2-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide;
1-Ethyl-1H-pyrazole-4-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide;
2,3-Dimethyl-3H-imidazole-4-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide;
1,5-Dimethyl-1H-pyrazole-4-sulfonic acid (3-amino-4-benzyl-chroman-6-ylmethyl)-amide;
cis-N-(-4-Benzyl-3-methylamino-chroman-6-ylmethyl)-methanesulfonamide;
trans-N-(-4-Benzyl-3-methylamino-chroman-6-ylmethyl)-methanesulfonamide;

cis-1-Methyl-1H-imidazole-4-sulfonic acid (-4-benzyl-3-pyrrolidin-1-yl-chroman-6-ylmethyl)-amide;
cis-Ethanesulfonic acid (-4-benzyl-3-pyrrolidin-1-yl-chroman-6-ylmethyl)-amide;
cis-N-(-4-Benzyl-3-pyrrolidin-1-yl-chroman-6-ylmethyl)-methanesulfonamide;
cis-N-(-4-Benzyl-3-pyrrolidin-1-yl-chroman-6-ylmethyl)-C-cyclopropyl-methanesulfonamide;
cis-1-Methyl-1H-pyrazole-4-sulfonic acid (-4-benzyl-3-pyrrolidin-1-yl-chroman-6-ylmethyl)-amide;
cis-N-(-3-Amino-4-benzyl-chroman-6-ylmethyl)-C-cyclopropyl-methanesulfonamide;
trans-N-(-3-Amino-4-benzyl-chroman-6-ylmethyl)-C-cyclopropyl-methanesulfonamide;
cis-Cyclobutanesulfonic acid (-3-amino-4-benzyl-chroman-6-ylmethyl)-amide;
trans-Cyclobutanesulfonic acid (-3-amino-4-benzyl-chroman-6-ylmethyl)-amide;
cis-Propane-1-sulfonic acid (-3-amino-4-benzyl-chroman-6-ylmethyl)-amide;
trans-Propane-1-sulfonic acid (-3-amino-4-benzyl-chroman-6-ylmethyl)-amide;
trans-Ethanesulfonic acid [2-(-4-benzyl-2,2-dimethyl-3-methylamino-chroman-6-yloxy)-ethyl]-amide;
cis-Propane-1-sulfonic acid [2-(-4-benzyl-2,2-dimethyl-3-methylamino-chroman-6-yloxy)-ethyl]-amide;
trans-Propane-1-sulfonic acid [2-(-4-benzyl-2,2-dimethyl-3-methylamino-chroman-6-yloxy)-ethyl]-amide;
cis-N-[2-(-4-Benzyl-2,2-dimethyl-3-methylamino-chroman-6-yloxy)-ethyl]-C-cyclopropyl-methanesulfonamide;
trans-N-[2-(-4-Benzyl-2,2-dimethyl-3-methylamino-chroman-6-yloxy)-ethyl]-C-cyclopropyl-methanesulfonamide;
cis-Ethanesulfonic acid [2-(-4-benzyl-2,2-dimethyl-3-methylamino-chroman-6-yloxy)-ethyl]-amide,
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.

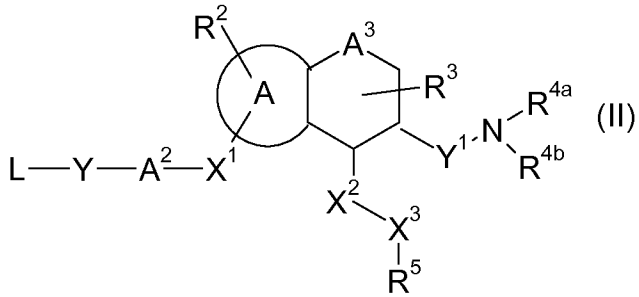
36. The method, use or compound as claimed in any one of claims 30 to 35, wherein the disorder is associated with glycinergic or glutamatergic neurotransmission dysfunction.

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.

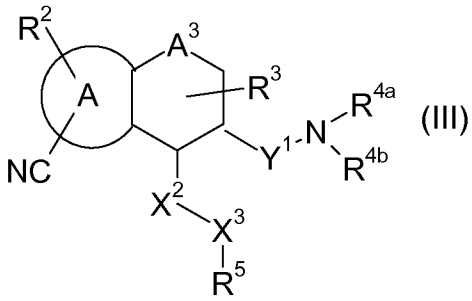
40. Compounds of the formula (II)



(II)

wherein L is an amino-protecting group, Y is NR^9, and A^2, X^1, A, R^2, A^3, R^3, Y^1, R^{4a}, R^{4b}, X^2, X^3, R^5, R^9 are defined as in any one of claims 1 to 28.

41. Compounds of the formula (III)



wherein A, R^2, A^3, R^3, Y^1, R^{4a}, R^{4b}, X^2, X^3, R^5 are defined as in any one of claims 1 to 28.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/065294

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D311/58 C07D405/12 C07D407/12 C07D409/12 A61K31/352
A61P25/02 A61P25/04 A61P25/18 A61P25/28
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	WO 00/07978 A1 (AKZO NOBEL NV [NL]; GIBSON SAMUEL GEORGE [GB]; JAAP DAVID ROBERT [GB];) 17 February 2000 (2000-02-17) claims 1,8,10	1-41
Y	WO 2005/123681 A1 (GRUENENTHAL GMBH [DE]; SUNDERMANN BERND [DE]; HENNIES HAGEN-HEINRICH []) 29 December 2005 (2005-12-29) claims 1,14,15	1-41

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

"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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 September 2012	21/09/2012

Name and mailing address of the ISA/	Authorized officer
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