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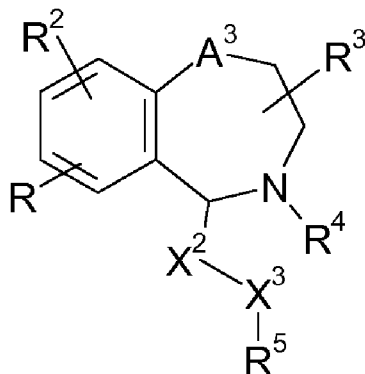
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(54) **Title:** BENZAZEPINE DERIVATIVES, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM, AND THEIR USE IN THERAPY



(I)

(57) **Abstract:** The present invention relates to benzazepine derivatives of the formula (I) or a physiologically tolerated salt thereof. The present invention also relates to pharmaceutical compositions comprising such benzazepine derivatives, and the use of such benzazepine derivatives for therapeutic purposes.

Benzazepine derivatives, pharmaceutical compositions containing them, and their use in therapy

Background of the Invention

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The present invention relates to benzazepine derivatives, pharmaceutical compositions comprising such benzazepine derivatives, and the use of such benzazepine derivatives for therapeutic purposes. The benzazepine derivatives are GlyT1 inhibitors.

10 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.

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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.

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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.

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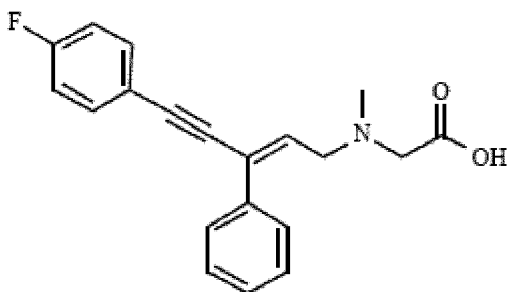
Molecular cloning has further revealed the existence of three variants of GlyT1, termed GlyT-1a, GlyT-1b and GlyT-1c, each of which displays a unique distribution in the brain and peripheral tissues. The variants arise by differential splicing and exon usage, and differ in their N-terminal regions.

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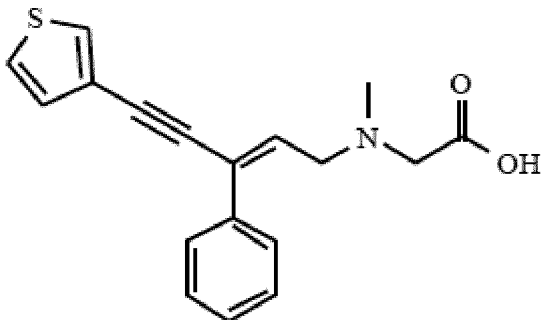
The physiological effects of GlyT1 in forebrain regions together with clinical reports showing the beneficial effects of GlyT1 inhibitor sarcosine in improving symptoms in schizophrenia patients suggest that selective GlyT1 inhibitors represent a new class of antipsychotic drugs.

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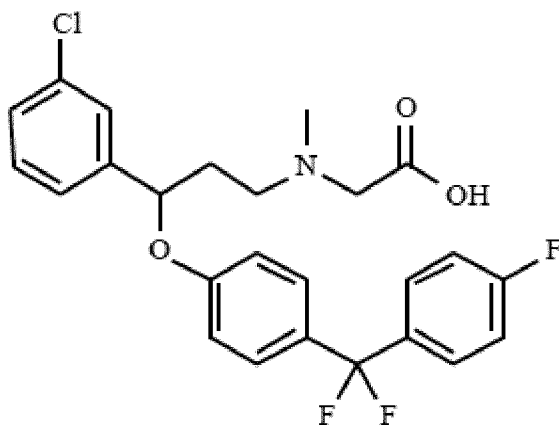
Glycine transporter inhibitors are already known in the art, for example:



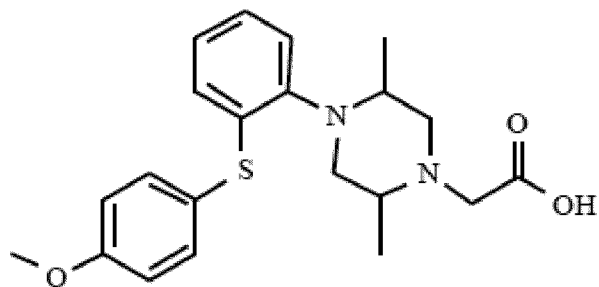
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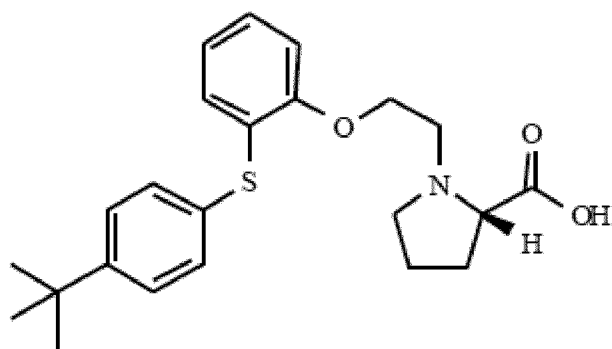
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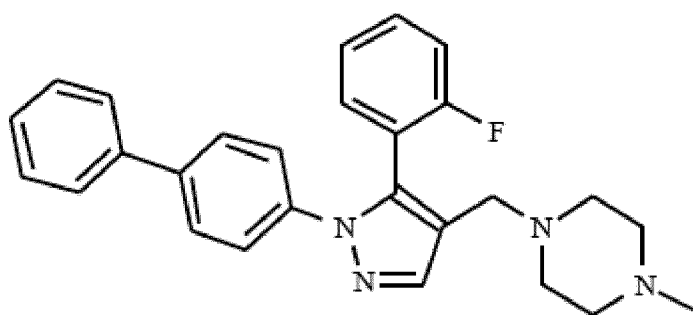
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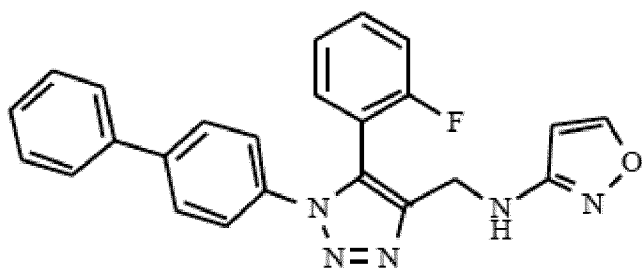
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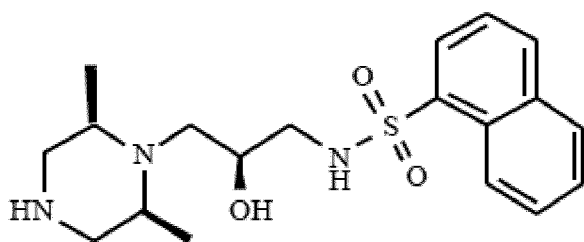
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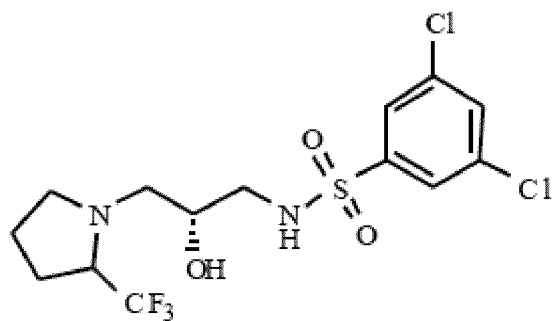
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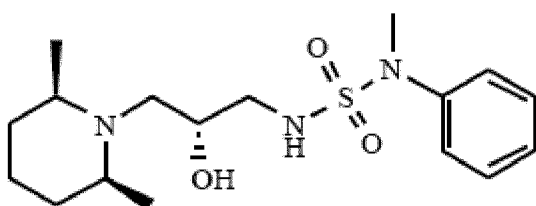
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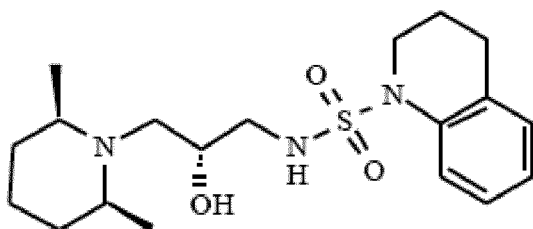
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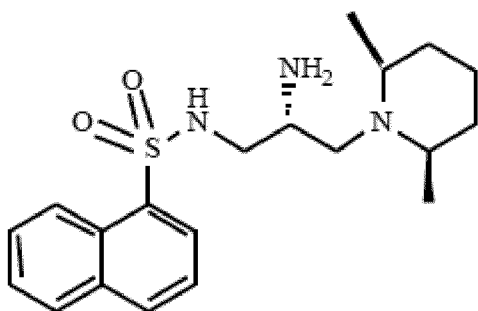
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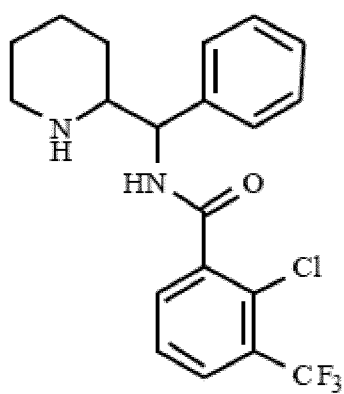
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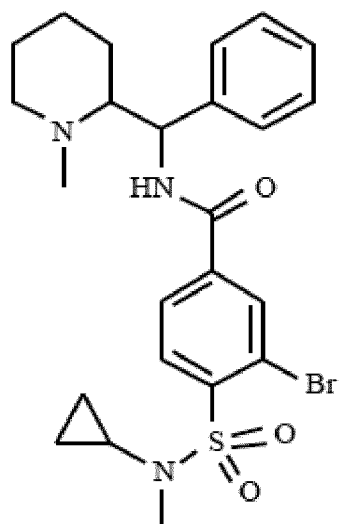
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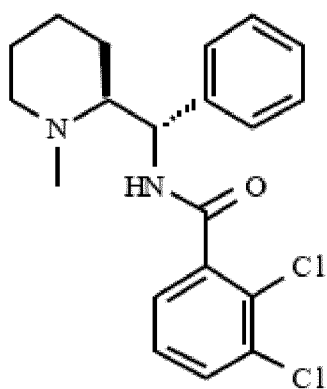
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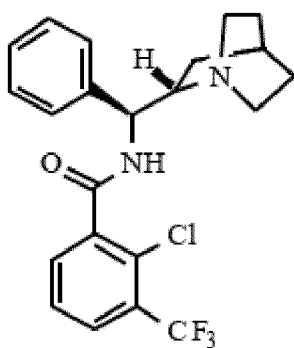
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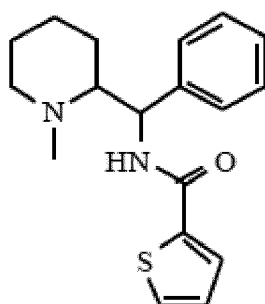
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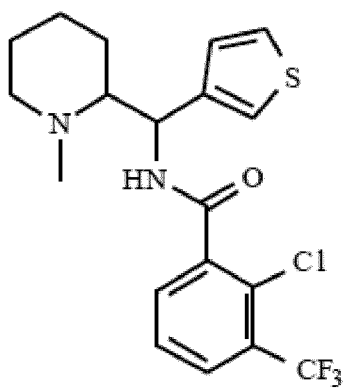
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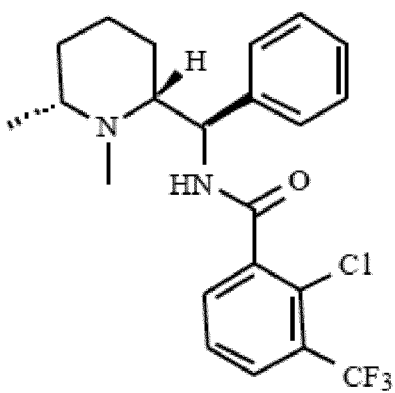
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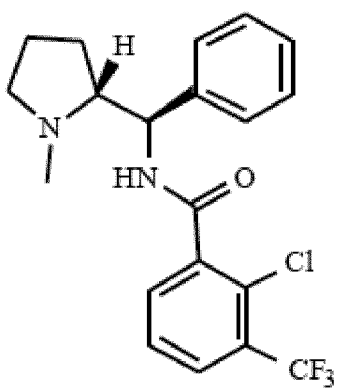
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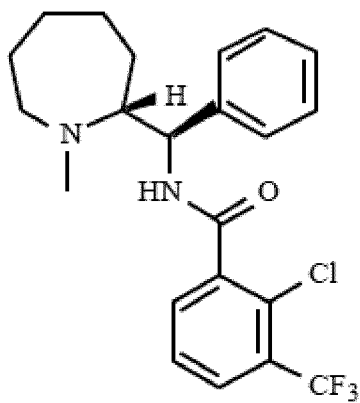
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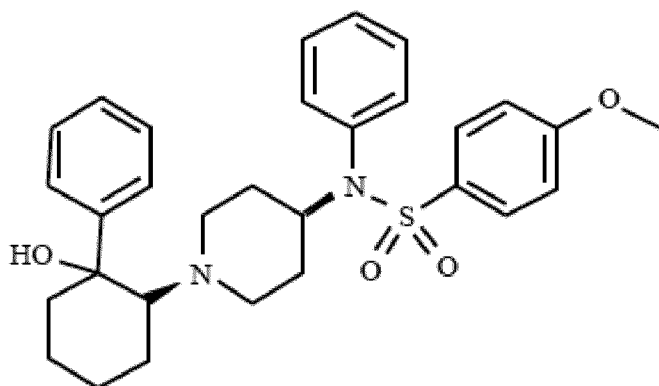
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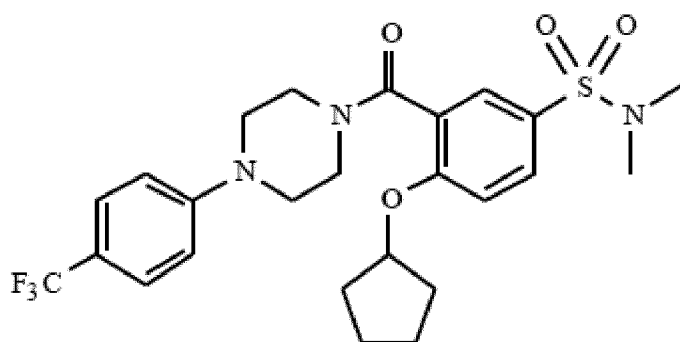
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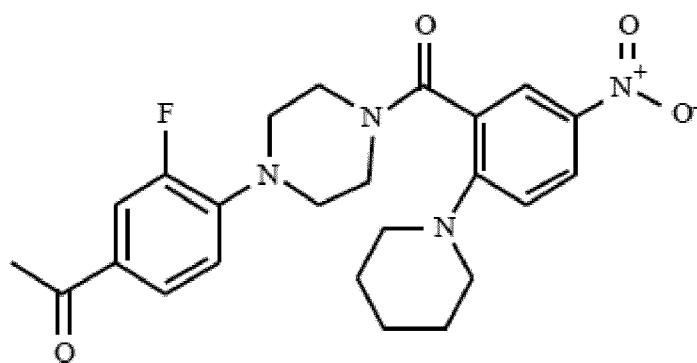
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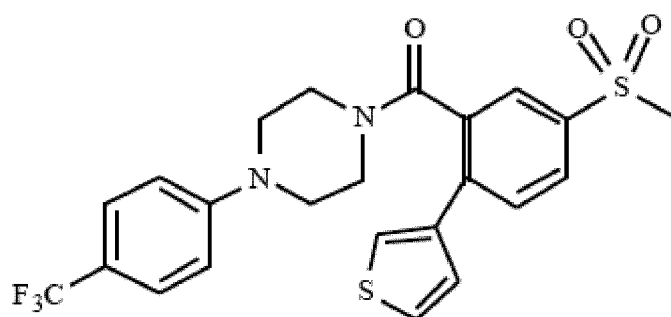
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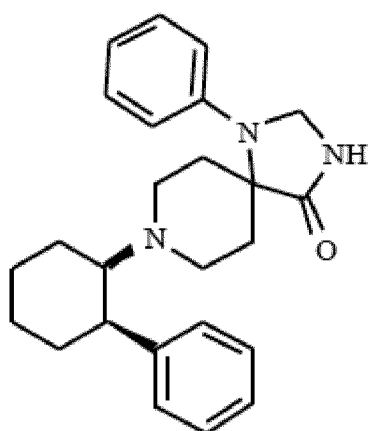
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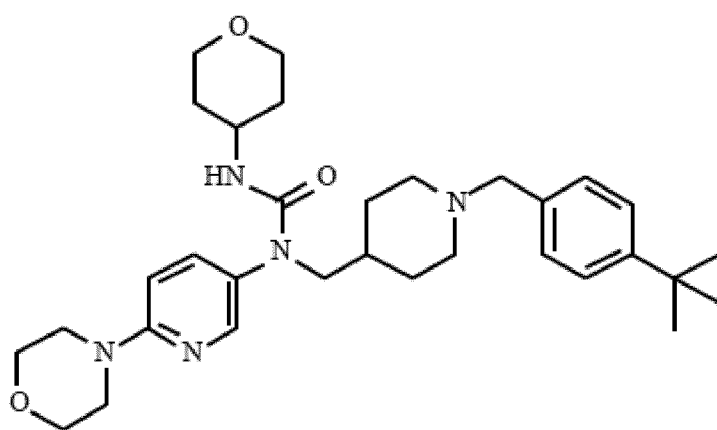
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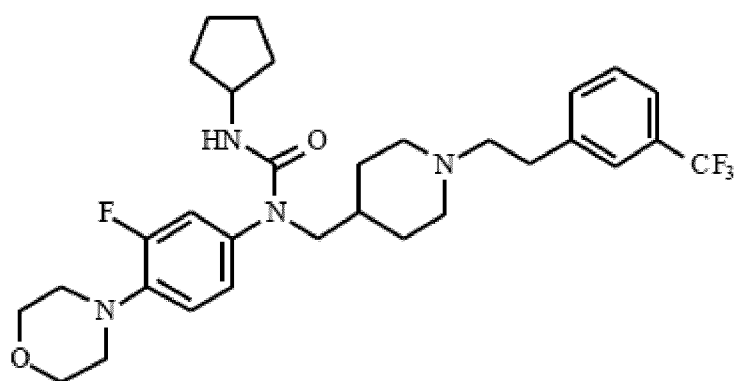
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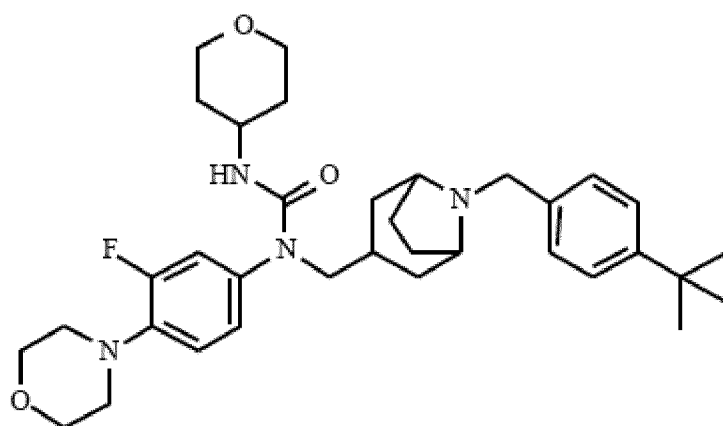
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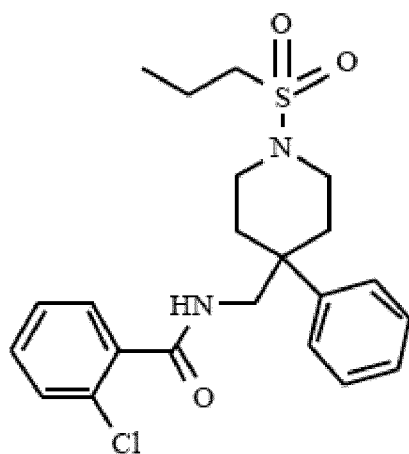
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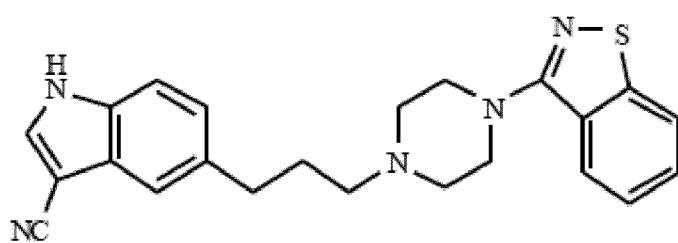
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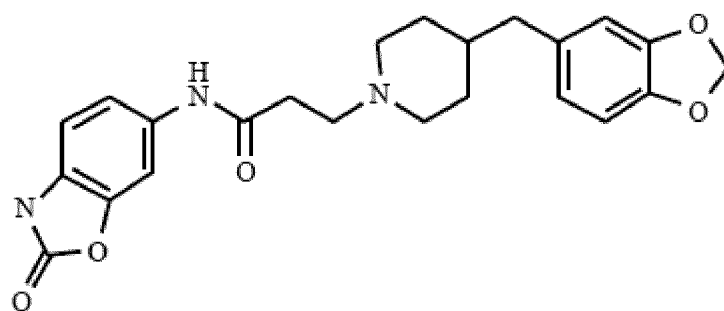
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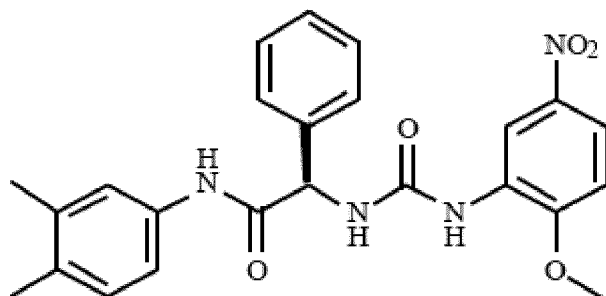
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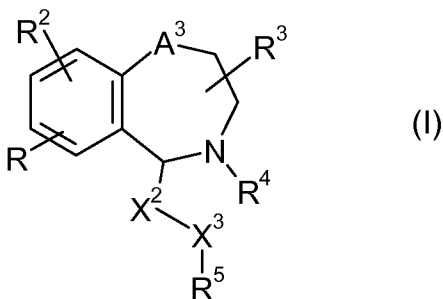
WO 2004022528

(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.

10 Summary of the Invention

The present invention relates to benzazepine derivatives of the formula (I)



15

wherein

R is R¹-W-A¹-Q-Y-A²-X¹- or -CN;

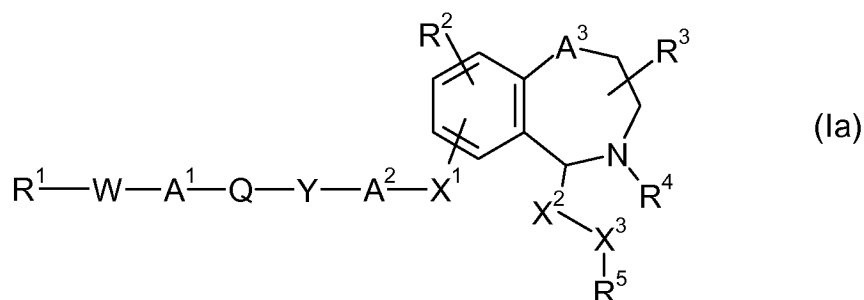
20 R¹ is hydrogen, alkyl, cycloalkylalkyl, halogenated alkyl, trialkylsilylalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkylcarbonylaminoalkyl, alkyloxycarbonylaminoalkyl, alkylaminocarbonylaminoalkyl, dialkylaminocarbonylaminoalkyl, alkylsulfonylaminoalkyl, (optionally substituted arylalkyl) aminoalkyl, optionally substituted arylalkyl, optionally substituted heterocyclalkyl, cycloalkyl, al-

- 5 kylcarbonyl, alkoxycarbonyl, halogenated alkoxycarbonyl, aryloxycarbonyl, amino-
 carbonyl, alkylaminocarbonyl, (halogenated alkyl)aminocarbonyl, arylaminocar-
 bonyl, alkenyl, alkynyl, optionally substituted aryl, hydroxy, alkoxy, halogenated
 alkoxy, hydroxyalkoxy, alkoxyalkoxy, aminoalkoxy, alkylaminoalkoxy, dialkylami-
 10 noalkoxy, alkylcarbonylaminoalkoxy, arylcarbonylaminoalkoxy, alkoxycarbonylami-
 noalkoxy, arylalkoxy, alkylsulfonylaminoalkoxy, (halogenated alkyl)sulfonylamino-
 alkoxy, arylsulfonylaminoalkoxy, (arylalkyl)sulfonylaminoalkoxy, heterocyclysulfon-
 ylaminalkoxy, heterocyclylalkoxy, aryloxy, heterocyclyloxy, alkylthio, halogenated
 15 alkylthio, alkylamino, (halogenated alkyl)amino, dialkylamino, di-(halogenated al-
 kyl)amino, alkylcarbonylamino, (halogenated alkyl)carbonylamino, arylcarbonyl-
 amino, alkylsulfonylamino, (halogenated alkyl)sulfonylamino, arylsulfonylamino or
 optionally substituted heterocyclyl;
- 20 W is -NR⁸- or a bond;
- 15 A¹ is optionally substituted alkylene or a bond;
- Q is -S(O)₂- or -C(O)-;
- 20 Y is -NR⁹- or a bond;
- 25 A² is optionally substituted alkylene, alkylene-CO-, -CO-alkylene, alkylene-O-alkylene,
 alkylene-NR¹⁰-alkylene, optionally substituted alkenylene, optionally substituted al-
 kynylene, optionally substituted arylene, optionally substituted heteroarylene or a
 bond;
- 30 X¹ is -O-, -NR¹¹-, -S-, optionally substituted alkylene, optionally substituted alkenylen,
 optionally substituted alkynylene;
- 35 R² is hydrogen, halogen, alkyl, halogenated alkyl, hydroxyalkyl, -CN, alkenyl, alkynyl,
 optionally substituted aryl, hydroxy, alkoxy, halogenated alkoxy, alkoxycarbonyl, al-
 kenyloxy, arylalkoxy, alkylcarbonyloxy, alkylthio, alkylsulfinyl, alkylsulfonyl, amino-
 sulfonyl, amino, alkylamino, alkenylamino, nitro or optionally substituted heterocyc-
 cycl, or two radicals R² together with the ring atoms of A to which they are bound
 form a 5- or 6-membered ring;

- A^3 is $-CH_2-$, $-O-$, $-NR^{16}-$, or $-S-$;
- 5 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;
- R^4 is hydrogen, alkyl, cycloalkylalkyl, halogenated alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, CH_2CN , arylalkyl, cycloalkyl, $-CHO$, alkylcarbonyl, (halogenated alkyl)carbonyl, arylcarbonyl, alkoxycarbonyl, aryloxy carbonyl, alkylaminocarbonyl, alkenyl, $-C(=NH)NH_2$, $-C(=NH)NHCN$, alkylsulfonyl, arylsulfonyl, amino, $-NO$ or heterocyclyl;
- 10 X^2 is $-O-$, $-NR^6-$, $-S-$, $>CR^{12a}R^{12b}$ or a bond;
- 15 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;
- 20 R^6 is hydrogen or alkyl;
- R^7 is hydrogen or alkyl;
- R^8 is hydrogen or alkyl;
- 25 R^9 is hydrogen, alkyl, cycloalkyl, aminoalkyl, optionally substituted arylalkyl or heterocyclyl; or
- R^9, R^1
- 30 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;
- 35 R^{10} is hydrogen, alkyl or alkylsulfonyl;

- R^{11} is hydrogen or alkyl, or
- 5 R^9, R^{11} together are alkylene,
- R^{12a} is hydrogen, optionally substituted alkyl, alkylaminoalkyl, dialkylaminoalkyl, heterocyclalkyl, optionally substituted aryl or hydroxy;
- 10 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 $-NR^{14}-$;
- 15 R^{13a} is hydrogen, optionally substituted alkyl, alkylaminoalkyl, dialkylaminoalkyl, heterocyclalkyl, optionally substituted aryl or hydroxy;
- R^{13b} is hydrogen or alkyl, or
- 20 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 $-NR^{15}-$;
- 25 R^{14} is hydrogen or alkyl;
- R^{15} is hydrogen or alkyl; and
- 30 R^{16} is hydrogen, alkyl, cycloalkylalkyl, halogenated alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, CH_2CN , arylalkyl, cycloalkyl, $-CHO$, alkylcarbonyl, (halogenated alkyl)carbonyl, arylcarbonyl, alkoxycarbonyl, aryloxy carbonyl, alkylaminocarbonyl, alkenyl, $-C(=NH)NH_2$, $-C(=NH)NHCN$, alkylsulfonyl, arylsulfonyl, amino, $-NO$ or heterocycl, or a physiologically tolerated salt thereof.
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Thus, the present invention relates to benzazepine derivatives having the formula (Ia)

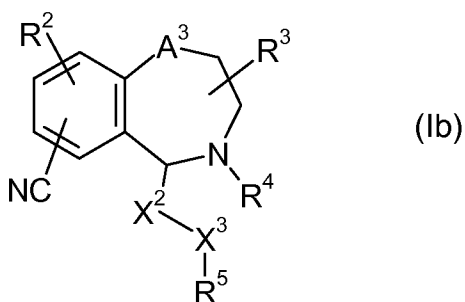


5

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

Further, the present invention relates to benzazepine derivatives of formula (I) wherein R is $-CN$, i.e. benzazepine derivatives having the formula (Ib)

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15

wherein R^2 , A^3 , R^3 , R^4 , X^2 , X^3 , R^5 are as defined herein.

Thus, the term benzazepine derivative is used herein to denote in particular benzazepines and benzazepine derivatives wherein the fused heterocyclic ring contains a further heteroatom.

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Said compounds of formula (I), i.e., the benzazepine derivatives of formula (I) and their physiologically tolerated salts, are glycine transporter inhibitors and thus useful as pharmaceuticals. The compounds of formula (I) display good to moderate metabolic stability.

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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 benzazepine 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.

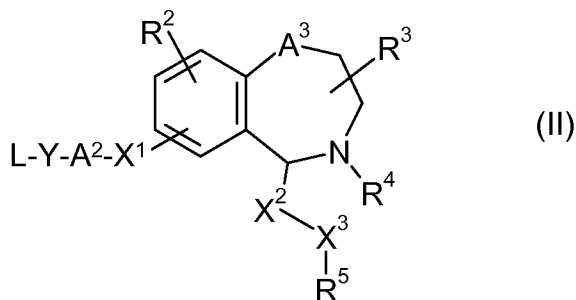
Glycine transport inhibitors and in particular inhibitors of the glycine transporter GlyT1 are known to be useful in treating a variety of neurologic and psychiatric disorders.

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 benzazepines derivatives of formula (II):



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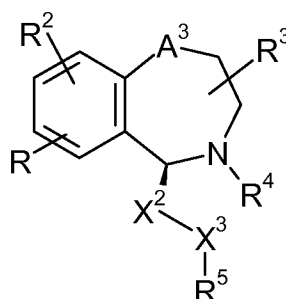
wherein L is an amino-protecting group, Y is NR⁹, and A², X¹, R², A³, R³, R⁴, X², X³, R⁵ are defined as herein.

Detailed description of the Invention

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

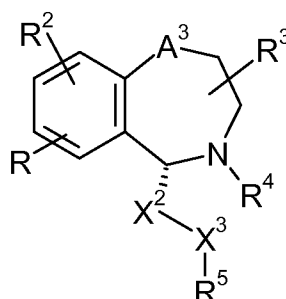
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According to one embodiment, an enantiomer of the benzazepine derivatives of the present invention has the following formula:



15 wherein R, R², A³, R³, R⁴, X², X³, R⁵ are as defined herein.

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



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wherein R, R², A³, R³, R⁴, X², X³, R⁵ are as defined herein.

The physiologically tolerated salts of the benzazepine derivatives of the formula (I) are especially acid addition salts with physiologically tolerated acids. Examples of suitable physiologically tolerated organic and inorganic acids are hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, C₁-C₄-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 ac-

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- ids 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 benzazepine derivatives also include salts of a physiologically tolerated anion with an benzazepine derivatives wherein one or more than one nitrogen atom is quaternized, e.g. with an alkyl residue (e.g. methyl or ethyl).
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- 10 The present invention moreover relates to compounds of formula (I) as defined herein, wherein at least one of the atoms has been replaced by its stable, non-radioactive isotope (e.g., hydrogen by deuterium, ^{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.
- 15 Of course, such compounds contain more of the respective isotope than this naturally occurs and thus is anyway present in the compounds (I).
- Stable isotopes (e.g., deuterium, ^{13}C , ^{15}N , ^{18}O) are nonradioactive isotopes which contain one or more additional neutron than the normally abundant isotope of the respective atom.
- 20 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).
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- 30 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.
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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; Czajka D M et al., *Am. J. Physiol.* 1961 201: 357). Higher deuterium concentrations, usually in excess of 20%, can be toxic in animals. However, acute replacement of as high as 15%-23% of the hydrogen in humans' fluids with deuterium was found not to cause toxicity (Blagojevic N et al. in "Dosimetry & Treatment Planning for

Neutron Capture Therapy", Zamenhof R, Solares G and Harling O Eds. 1994. Advanced Medical Publishing, Madison Wis. pp.125-134; Diabetes Metab. 23: 251 (1997)).

5 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 %.

10 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 deuterio acid such as D₂SO₄/D₂O. Alternatively, deuterium atoms may be incorporated in various combinations during the synthesis of compounds of the invention. Certain hydrogen atoms are not easily exchange-
15 able 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.

20 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*,
25 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.
30 20090137457; 20090131485; 20090131363; 20090118238; 20090111840; 20090105338; 20090105307; 20090105147; 20090093422; 20090088416; 20090082471, the methods are hereby incorporated by reference.

35 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.

40 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, C₁-C₄-alkyl, hydroxy-C₁-C₄-alkyl, C₃-C₁₂-heterocyclyl-alkyl, C₁-C₄-alkoxy-

C₁-C₄-alkyl, amino-C₁-C₄-alkyl, C₁-C₄-alkenyl, OH, SH, CN, CF₃, O-CF₃, COOH, O-CH₂-COOH, C₁-C₆-alkoxy, C₁-C₆-alkylthio, C₃-C₇-cycloalkyl, COO-C₁-C₆-alkyl, CONH₂, CONH-C₁-C₆-alkyl, SO₂NH-C₁-C₆-alkyl, CON-(C₁-C₆-alkyl)₂, SO₂N-(C₁-C₆-alkyl)₂, NH₂, NH-C₁-C₆-alkyl, N-(C₁-C₆-alkyl)₂, NH-(C₁-C₄-alkyl-C₆-C₁₂-aryl), NH-CO-C₁-C₆-alkyl, NH-SO₂-C₁-C₆-alkyl, SO₂-C₁-C₆-alkyl, C₆-C₁₂-aryl, O-C₆-C₁₂-aryl, O-CH₂-C₆-C₁₂-aryl, CONH-C₆-C₁₂-aryl, SO₂NH-C₆-C₁₂-aryl, CONH-C₃-C₁₂-heterocyclyl, SO₂NH-C₃-C₁₂-heterocyclyl, SO₂-C₆-C₁₂-aryl, NH-SO₂-C₆-C₁₂-aryl, NH-CO-C₆-C₁₂-aryl, NH-SO₂-C₃-C₁₂-heterocyclyl, NH-CO-C₃-C₁₂-heterocyclyl and C₃-C₁₂-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, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy and C₁-C₄-haloalkoxy.

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

- 15 C₁-C₄-Alkyl is a straight-chain or branched alkyl group having from 1 to 4 carbon atoms. Examples of an alkyl group are methyl, C₂-C₄-alkyl such as ethyl, n-propyl, iso-propyl, n-butyl, 2-butyl, iso-butyl or tert-butyl. C₁-C₂-Alkyl is methyl or ethyl, C₁-C₃-alkyl is additionally n-propyl or isopropyl.
- 20 C₁-C₆-Alkyl is a straight-chain or branched alkyl group having from 1 to 6 carbon atoms. Examples include methyl, C₂-C₄-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.
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- Halogenated C₁-C₄-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, wherein 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-
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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 C₁-C₄ alkyl groups as defined, such as trifluoromethyl.

- 5 C₆-C₁₂-Aryl-C₁-C₄-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in particular 1 or two carbon atoms, wherein one hydrogen atom is replaced by C₆-C₁₂-aryl, such as in benzyl.
- 10 Hydroxy-C₁-C₄-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, wherein one or two hydrogen atoms are replaced by one or two hydroxyl groups, such as in hydroxymethyl, (R)-1-hydroxyethyl, (S)-1-hydroxyethyl, 2-hydroxyethyl, (R)-1-hydroxypropyl, (S)-1-hydroxypropyl, 2-hydroxypropyl, 3-hydroxypropyl, (R)-2-hydroxy-1-methylethyl, (S)-2-hydroxy-1-methylethyl, 2-hydroxy-1-(hydroxymethyl)ethyl, (R)-1-hydroxybutyl, (S)-1-hydroxybutyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl.

- C₁-C₆-Alkoxy-C₁-C₄-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, wherein one or two hydrogen atoms are replaced by one or two 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.

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

- 35 C₁-C₆-Alkylamino-C₁-C₄-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in particular 1 or two carbon atoms, wherein one hydrogen atom is replaced by a C₁-C₆-alkylamino group, in particular by a C₁-C₄-alkylamino group, such as in methylami-

nomethyl, ethylaminomethyl, n-propylaminomethyl, iso-propylaminomethyl, n-butylaminomethyl, 2-butylaminomethyl, iso-butylaminomethyl or tert-butylaminomethyl.

- 5 Di-C₁-C₆-Alkylamino-C₁-C₄-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in particular 1 or two carbon atoms, wherein one hydrogen atom is replaced by a di-C₁-C₆-Alkylamino group, in particular by a di-C₁-C₄-alkylamino group, such as in dimethylaminomethyl.
- 10 C₁-C₆-Alkylcarbonylamino-C₁-C₄-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in particular 1 or two carbon atoms, wherein one hydrogen atom is replaced by a C₁-C₆-alkylcarbonylamino group, in particular by a C₁-C₄-alkylcarbonylamino group, such as in methylcarbonylaminoethyl, ethylcarbonylaminoethyl, n-propylcarbonylaminoethyl, 15 iso-propylcarbonylaminoethyl, n-butylcarbonylaminoethyl, 2-butylcarbonylaminoethyl, iso-butylcarbonylaminoethyl or tert-butylcarbonylaminoethyl.
- 20 C₁-C₆-Alkylaminocarbonylamino-C₁-C₄-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in particular 1 or two carbon atoms, wherein one hydrogen atom is replaced by a C₁-C₆-alkylaminocarbonylamino group, in particular by a C₁-C₄-alkylaminocarbonylamino group, such as in methylaminocarbonylaminoethyl, ethylaminocarbonylaminoethyl, n-propylaminocarbonylaminoethyl, iso-propylaminocarbonylaminoethyl, n- 25 butylaminocarbonylaminoethyl, 2-butylaminocarbonylaminoethyl, iso-butylaminocarbonylaminoethyl or tert-butylaminocarbonylaminoethyl.
- 30 Di-C₁-C₆-alkylaminocarbonylamino-C₁-C₄-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in particular 1 or two carbon atoms, wherein one hydrogen atom is replaced by a di-C₁-C₆-alkylaminocarbonylamino group, in particular by a di-C₁-C₄-alkylaminocarbonylamino group, such as in dimethylaminocarbonylaminoethyl, dimethylaminocarbonyl- 35 aminoethyl, dimethylaminocarbonylamino-n-propyl.
- C₁-C₆-Alkylsulfonylamino-C₁-C₄-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in particular 1 or two carbon atoms, wherein one hydrogen atom is replaced by a C₁-C₆-alkylsulfonylamino group, in particular by a C₁-C₄-alkylsulfonylamino group, such as in methylsulfonylaminoethyl, ethylsulfonylaminoethyl, n-propylsulfonylaminoethyl, iso-

propylsulfonylaminomethyl, n-butylsulfonylaminomethyl, 2-butylsulfonylaminomethyl, isobutylsulfonylaminomethyl or tert-butylsulfonylaminomethyl.

- (C₆-C₁₂-Aryl-C₁-C₆-alkyl)amino-C₁-C₄ alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in particular 1 or two carbon atoms, wherein one hydrogen atom is replaced by a (C₆-C₁₂-aryl-C₁-C₆-alkyl)amino group, in particular a (C₆-C₁₂-aryl-C₁-C₂-alkyl)amino group, such as in benzylaminomethyl.
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- 10 C₃-C₁₂-Heterocyclyl-C₁-C₄-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in particular 1 or two carbon atoms, wherein one hydrogen atom is replaced by C₃-C₁₂-heterocyclyl, such as in N-pyrrolidinylmethyl, N-piperidinylmethyl, N-morpholinylmethyl.
- 15 C₃-C₁₂-Cycloalkyl is a cycloaliphatic radical having from 3 to 12 carbon atoms. In particular, 3 to 6 carbon atoms form the cyclic structure, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The cyclic structure may be unsubstituted or may carry 1, 2, 3 or 4 C₁-C₄ alkyl radicals, preferably one or more methyl radicals.
- 20 Carbonyl is >C=O.
- C₁-C₆-Alkylcarbonyl is a radical of the formula R-C(O)-, wherein R is an alkyl radical having from 1 to 6, preferably from 1 to 4, in particular 1 or 2 carbon atoms as defined herein. Examples include acetyl, propionyl, n-butyryl, 2-methylpropionyl, pivaloyl.
- 25 Halogenated C₁-C₆-alkylcarbonyl is C₁-C₆-alkylcarbonyl as defined herein, wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by 1, 2, 3, 4 or a corresponding number of identical or different halogen atoms. Examples include fluoromethylcarbonyl, difluoromethylcarbonyl, trifluoromethylcarbonyl. Further examples are 1,1,1-trifluoroeth-2-ylcarbonyl, 1,1,1-trifluoroprop-3-ylcarbonyl.
- 30 C₆-C₁₂-Arylcarbonyl is a radical of the formula R-C(O)-, wherein R is an aryl radical having from 6 to 12 carbon atoms as defined herein. Examples include benzoyl.
- 35 C₁-C₆-Alkoxy carbonyl is a radical of the formula R-O-C(O)-, wherein R is an alkyl radical having from 1 to 6, preferably from 1 to 4, in particular 1 or 2 carbon atoms as defined herein. Examples include methoxycarbonyl and tert-butyloxycarbonyl.

Halogenated C₁-C₆-alkoxycarbonyl is a C₁-C₆-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.

- 5 C₆-C₁₂-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 phenoxy carbonyl.

Cyano is -C≡N.

- 10 Aminocarbonyl is NH₂C(O)-.

C₁-C₆-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.

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

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

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

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

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

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

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

5 C₆-C₁₂-Aryl is a 6- to 12-membered, in particular 6- to 10-membered, aromatic cyclic radical. Examples include phenyl and naphthyl.

C₃-C₁₂-Arylene is an aryl diradical. Examples include phen-1,4-ylene and phen-1,3-ylene.

Hydroxy is -OH.

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C₁-C₆-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-
15 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-
20 methylpropoxy.

Halogenated C₁-C₆-alkoxy is a straight-chain or branched alkoxy group having from 1 to 6, preferably from 1 to 4, in particular 1 or 2 carbon atoms, wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by 1, 2, 3, 4 or a corresponding number of
25 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-
35 halogenobutoxy, 3-halogenobutoxy, 4-halogenobutoxy, 1,1-dihalogenobutoxy, 2,2-dihalogenobutoxy, 3,3-dihalogenobutoxy, 4,4-dihalogenobutoxy, 4,4,4-trihalogenobutoxy, etc. Particular examples include the fluorinated C₁-C₄ alkoxy groups as defined, such as trifluoromethoxy.

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

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C₁-C₆-Alkoxy-C₁-C₄-alkoxy is an alkoxy radical having from 1 to 4 carbon atoms, preferably 1 or 2 carbon atoms as defined herein, wherein one or two hydrogen atoms are replaced by one or two alkoxy radicals having from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein. Examples include methoxymethoxy, 2-methoxyethoxy, 1-methoxyethoxy, 3-methoxypropoxy, 2-methoxypropoxy, 1-methyl-1-methoxyethoxy, ethoxymethoxy, 2-ethoxyethoxy, 1-ethoxyethoxy, 3-ethoxypropoxy, 2-ethoxypropoxy, 1-methyl-1-ethoxyethoxy and the like.

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Amino-C₁-C₄-alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by an amino group. Examples include 2-aminoethoxy.

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C₁-C₆-Alkylamino-C₁-C₄-alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by an alkylamino group having from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein. Examples include methylaminomethoxy, ethylaminomethoxy, n-propylaminomethoxy, isopropylaminomethoxy, n-butylaminomethoxy, 2-butylaminomethoxy, isobutylaminomethoxy, 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.

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Di-C₁-C₆-alkylamino-C₁-C₄-alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by a 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.

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C₁-C₆-Alkylcarbonylamino-C₁-C₄-alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by an 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, isopropylcarbonylaminomethoxy, n-butylcarbonylaminomethoxy, 2-

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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-butylcarbonyl-

5 amino)ethoxy, 2-(tert-butylcarbonylamino)ethoxy.

C₆-C₁₂-Arylcarbonylamino-C₁-C₄-alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by a C₆-C₁₂-arylcarbonylamino group as defined herein. Examples include 2-

10 (benzoylamino)ethoxy.

C₁-C₆-Alkoxy carbonylamino-C₁-C₄-alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by an alkoxy carbonylamino group wherein the alkoxy group has from 1 to 6, preferably from 1 to

15 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-(ethoxycarbonyl-

20 amino)ethoxy, 2-(n-propoxycarbonylamino)ethoxy, 2-(iso-propoxycarbonylamino)ethoxy, 2-(n-butoxycarbonylamino)ethoxy, 2-(2-butoxycarbonylamino)ethoxy, 2-(iso-butoxycarbonylamino)ethoxy, 2-(tert-butoxycarbonylamino)ethoxy.

C₂-C₆-Alkenyloxy is a radical of the formula R-O-, wherein R is a straight-chain or

25 branched alkenyl group having from 2 to 6, in particular 2 to 4 carbon atoms. Examples include vinyloxy, allyloxy (2-propen-1-yloxy), 1-propen-1-yloxy, 2-propen-2-yloxy, methallyloxy (2-methylprop-2-en-1-yloxy) and the like. C₃-C₅-Alkenyloxy is, in particular, allyloxy, 1-methylprop-2-en-1-yloxy, 2-buten-1-yloxy, 3-buten-1-yloxy, methallyloxy, 2-penten-1-yloxy, 3-penten-1-yloxy, 4-penten-1-yloxy, 1-methylbut-2-en-1-yloxy or 2-ethylprop-2-en-1-

30 yloxy.

C₆-C₁₂-Aryl-C₁-C₄-alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by a C₆-C₁₂-aryl group as defined herein. Examples include benzyloxy.

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

40 [(2-methylpropyl)sulfonylamino]ethoxy.

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

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

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

C₃-C₁₂-Heterocyclylsulfonylamino-C₁-C₄-alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by a C₃-C₁₂-heterocyclylsulfonylamino group as defined herein. Examples include 2-(pyridin-3-yl-sulfonylamino)ethoxy.

C₃-C₁₂-Heterocyclyl-C₁-C₄-alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by a C₃-C₁₂-heterocyclyl group as defined herein. Examples include 2-(N-pyrrolidinyl)ethoxy, 2-(N-morpholinyl)ethoxy and 2-(N-imidazolyl)ethoxy.

C₁-C₂-Alkylenedioxy 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 methylenedioxy.

C₆-C₁₂-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.

C₃-C₁₂-Heterocyclyloxy is a radical of the formula R-O-, wherein R is a C₃-C₁₂-heterocyclyl group having from 3 to 12, in particular from 3 to 7 carbon atoms as defined herein. Examples include pyridin-2-yloxy.

C₁-C₆-Alkylthio is a radical of the formula R-S-, wherein R is an alkyl radical having from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein. Examples include methylthio,

ethylthio, propylthio, butylthio, pentylthio, 1-methylbutylthio, 2-methylbutylthio, 3-methylbutylthio, 2,2-dimethylpropylthio, 1-ethylpropylthio, hexylthio, 1,1-dimethylpropylthio, 1,2-dimethylpropylthio, 1-methylpentylthio, 2-methylpentylthio, 3-methylpentylthio, 4-methylpentylthio, 1,1-dimethylbutylthio, 1,2-dimethylbutylthio, 1,3-dimethylbutylthio, 2,2-dimethylbutylthio, 2,3-dimethylbutylthio, 3,3-dimethylbutylthio, 1-ethylbutylthio, 2-ethylbutylthio, 1,1,2-trimethylpropylthio, 1,2,2-trimethylpropylthio, 1-ethyl-1-methylpropyl and 1-ethyl-2-methylpropyl.

Halogenated C₁-C₆-alkylthio is a radical of the formula R-S-, wherein R is a halogenated alkyl radical having from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein. Examples include halogenomethylthio, dihalogenomethylthio, trihalogenomethylthio, (R)-1-halogenoethylthio, (S)-1-halogenoethylthio, 2-halogenoethylthio, 1,1-dihalogenoethylthio, 2,2-dihalogenoethylthio, 2,2,2-trihalogenoethylthio, (R)-1-halogenopropylthio, (S)-1-halogenopropylthio, 2-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 C₁-C₄ alkylthio groups as defined, such as trifluoromethylthio.

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

C₁-C₆-Alkylsulfonyl is a radical of the formula R-S(O)₂-, wherein R is an alkyl radical having from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein. Examples include methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, pentylsulfonyl, 1-

- methylbutylsulfonyl, 2-methylbutylsulfonyl, 3-methylbutylsulfonyl, 2,2-dimethylpropylsulfonyl, 1-ethylpropylsulfonyl, hexylsulfonyl, 1,1-dimethylpropylsulfonyl, 1,2-dimethylpropylsulfonyl, 1-methylpentylsulfonyl, 2-methylpentylsulfonyl, 3-methylpentylsulfonyl, 4-methylpentylsulfonyl, 1,1-dimethylbutylsulfonyl, 1,2-dimethylbutylsulfonyl, 1,3-dimethylbutylsulfonyl, 2,2-dimethylbutylsulfonyl, 2,3-dimethylbutylsulfonyl, 3,3-dimethylbutylsulfonyl, 1-ethylbutylsulfonyl, 2-ethylbutylsulfonyl, 1,1,2-trimethylpropylsulfonyl, 1,2,2-trimethylpropylsulfonyl, 1-ethyl-1-methylpropyl and 1-ethyl-2-methylpropyl.
- 10 (Halogenated C₁-C₆-alkyl)sulfonyl is a C₁-C₆-alkylsulfonyl as defined herein, wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by 1, 2, 3, 4 or a corresponding number of identical or different halogen atoms.
- 15 C₆-C₁₂-Arylsulfonyl is a radical of the formula R-S(O)₂·, wherein R is an aryl radical having from 6 to 12 carbon atoms as defined herein. Examples include phenylsulfonyl.
- (C₆-C₁₂-Aryl-C₁-C₄-alkyl)sulfonyl is a radical of the formula R-S(O)₂·, wherein R is a C₆-C₁₂-aryl-C₁-C₄-alkyl radical, in particular a C₆-C₁₂-aryl-C₁-C₂-alkyl radical as defined herein. Examples include benzylsulfonyl.
- 20 C₃-C₁₂-Heterocyclylsulfonyl is a radical of the formula R-S(O)₂·, wherein R is C₃-C₁₂-heterocyclyl as defined herein.
- Aminosulfonyl is NH₂-S(O)₂·.
- 25 C₁-C₆-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, isopropylaminosulfonyl, n-butylaminosulfonyl, 2-butylaminosulfonyl, iso-butylaminosulfonyl, tert-butylaminosulfonyl.
- 30 Di-C₁-C₆-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.
- 35 C₆-C₁₂-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.
- 40 Amino is NH₂.

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

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

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

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

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

C₆-C₁₂-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.

C₂-C₆-Alkenylamino is a radical of the formula R-NH-, wherein R is a straight-chain or branched alkenyl group having from 2 to 6, in particular 2 to 4 carbon atoms. Examples include vinylamino, allylamino (2-propen-1-ylamino), 1-propen-1-ylamino, 2-propen-2-ylamino, methallylamino (2-methylprop-2-en-1-ylamino) and the like. C₃-C₅-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.

C₁-C₆-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, 5 tert-butylsulfonylamino.

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

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C₆-C₁₂-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.

15 Nitro is -NO₂.

C₃-C₁₂-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 20 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 25 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 C₃-C₁₂-heterocyclyl include:

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

C-bound, 5-membered, saturated rings, such as 35 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, 40

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;

- 5 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, 15 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
 20 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), hexahydro-25 pyridazin-1-yl, tetrahydro-1,3-oxazin-3-yl, tetrahydro-1,3-thiazin-3-yl, tetrahydro-1,4-thiazin-4-yl, tetrahydro-1,4-oxazin-4-yl (morpholin-1-yl), tetrahydro-1,2-oxazin-2-yl;

- C-bound, 5-membered, partially unsaturated rings, such as
 2,3-dihydrofuran-2-yl, 2,3-dihydrofuran-3-yl, 2,5-dihydrofuran-2-yl, 2,5-dihydrofuran-3-yl, 30 4,5-dihydrofuran-2-yl, 4,5-dihydrofuran-3-yl, 2,3-dihydrothien-2-yl, 2,3-dihydrothien-3-yl, 2,5-dihydrothien-2-yl, 2,5-dihydrothien-3-yl, 4,5-dihydrothien-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, 2,5-40 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-
 5 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-dihydro-
 10 thiazol-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-
 15 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-tetrahydropyridin-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-
 20 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,
 25 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-
 30 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-
 35 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-di-
 hydro-1,2-oxazin-5-yl, 4H-5,6-dihydro-1,2-oxazin-6-yl, 4H-5,6-dihydro-1,2-thiazin-3-yl, 4H-
 40 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-tetrahydropyridazin-5-yl, 1,2,5,6-tetrahydropyridazin-6-yl, 1,2,3,6-tetrahydropyridazin-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-tetrahydropyrimidin-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;
- 35 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;
- 40

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-
5 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-dihydro-1,4-thiazin-4-yl, 2H-
10 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
15 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, pyrrol-2-yl, pyrrol-3-yl, pyrazol-3-yl, pyrazol-4-yl, isoxa-
zol-3-yl, isoxazol-4-yl, isoxazol-5-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, imida-
zol-2-yl, imidazol-4-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, thiazol-2-yl, thiazol-4-yl, thia-
zol-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,
20 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-
25 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;

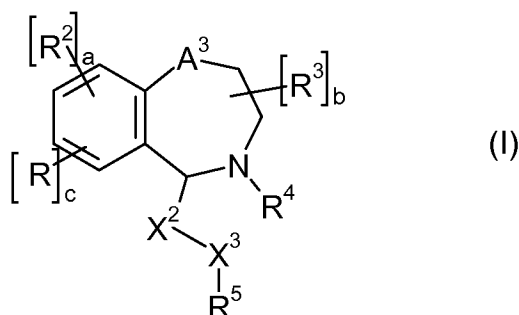
N-bound, 5-membered, heteroaromatic rings, such as
pyrrol-1-yl, pyrazol-1-yl, imidazol-1-yl, 1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, tetrazol-1-yl.
30

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 further anellated 5- or 6-membered heterocyclic ring, this heterocyclic ring being
35 saturated or unsaturated or aromatic. These include quinolinyl, isoquinolinyl, indolyl, indol-
iziny, isoindolyl, indazolyl, benzofuryl, benzthienyl, benzo[b]thiazolyl, benzoxazolyl,
benzthiazolyl and benzimidazolyl. Examples of 5- or 6-membered heteroaromatic com-
pounds comprising an anellated cycloalkenyl ring include dihydroindolyl, dihydroindoliz-
40 inyl, dihydroisoindolyl, dihydrochinolyl, dihydroisoquinolyl, chromenyl and chromanyl.

C₃-C₁₂-Heteroarylene is a heteroaryl diradical. Examples include pyrid-2,5-ylene and pyrid-2,4-ylene.

5 With respect to the compounds' capability of inhibiting glycine transporter 1, the variables R, R¹, W, A¹, Q, Y, A², X¹, R², A³, R³, R⁴, X², X³, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷ preferably have the following meanings which, when taken alone or in combination, represent particular embodiments of the benzazepine derivatives of the formula (I) or any other formula disclosed herein.

10 In said formula (I), there may be one or more than one substituent R, R² and/or R³. More particularly, there may be up to 3 substituents R², and up to 7 substituents R³. Preferably there is one substituent R and 1, 2 or 3 substituents R². Formula (I) may thus be depicted as follows:



15 wherein a is 1, 2 or 3, b is 1, 2, 3, 4, 5, 6 or 7 and c is 1. If there is more than one radical R², these may be the same or different radicals. If there is more than one radical R³, these may be the same or different radicals.

According to one embodiment, R is cyano.

20

Preferably, R is R¹-W-A¹-Q-Y-A²-X¹- and R¹, W, A¹, Q, Y, A², X¹, R², A³, R³, R⁴, X², X³, R⁵ are as defined herein.

25 R¹ is hydrogen, C₁-C₆-alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl or n-pentyl), C₃-C₁₂-cycloalkyl-C₁-C₄-alkyl (e.g. cyclopropylmethyl, cyclopentylmethyl or cyclohexylmethyl), halogenated C₁-C₆-alkyl (e.g. 3-fluoroprop-1-yl, 3-chloroprop-1-yl or 3,3,3-trifluoroprop-1-yl), tri-(C₁-C₄-alkyl)-silyl-C₁-C₄-alkyl (e.g. trimethylsilylethyl), hydroxy-C₁-C₄-alkyl, C₁-C₆-alkoxy-C₁-C₄-alkyl (e.g. ethoxyethyl), amino-C₁-C₄-alkyl, C₁-C₆-alkylamino-C₁-C₄-alkyl, di-C₁-C₆-alkylamino-C₁-C₄-alkyl, C₁-C₆-alkylcarbonylamino-C₁-C₄-alkyl, C₁-C₆-alkyloxycarbonylamino-C₁-C₄-alkyl, C₁-C₆-alkylaminocarbonylamino-C₁-C₄-alkyl, di-C₁-C₆-alkylaminocarbonylamino-C₁-C₄-alkyl, C₁-C₆-alkylsulfonylamino-C₁-C₄-alkyl, (optionally substituted C₆-C₁₂-aryl-C₁-C₆-alkyl)amino-C₁-C₄-alkyl, optionally substituted C₆-C₁₂-aryl-C₁-C₄-alkyl, optionally substituted C₃-C₁₂-heterocyclyl-C₁-C₄-alkyl, C₃-C₁₂-cycloalkyl (e.g.

30

- cyclopropyl or cyclobutyl), C₁-C₆-alkylcarbonyl, C₁-C₆-alkoxycarbonyl, halogenated C₁-C₆-alkoxycarbonyl, C₆-C₁₂-aryloxycarbonyl, aminocarbonyl, C₁-C₆-alkylaminocarbonyl, (halogenated C₁-C₄-alkyl)aminocarbonyl, C₆-C₁₂-arylaminocarbonyl, C₂-C₆-alkenyl (e.g. prop-1,2-en-1-yl), C₂-C₆-alkynyl, optionally substituted C₆-C₁₂-aryl (e.g. phenyl, 2-methylphenyl), hydroxy, C₁-C₆-alkoxy (e.g. tert-butyloxy), halogenated C₁-C₆-alkoxy, C₁-C₆-hydroxyalkoxy, C₁-C₆-alkoxy-C₁-C₄-alkoxy, amino-C₁-C₄-alkoxy, C₁-C₆-alkylamino-C₁-C₄-alkoxy, di-C₁-C₆-alkylamino-C₁-C₄-alkoxy, C₁-C₆-alkylcarbonylamino-C₁-C₄-alkoxy, C₆-C₁₂-arylcarbonylamino-C₁-C₄-alkoxy, C₁-C₆-alkoxycarbonylamino-C₁-C₄-alkoxy, C₆-C₁₂-aryl-C₁-C₄-alkoxy, C₁-C₆-alkylsulfonylamino-C₁-C₄-alkoxy, (halogenated C₁-C₆-alkyl)sulfonylamino-C₁-C₄-alkoxy, C₆-C₁₂-arylsulfonylamino-C₁-C₄-alkoxy, (C₆-C₁₂-aryl-C₁-C₆-alkyl)sulfonylamino-C₁-C₄-alkoxy, C₃-C₁₂-heterocyclylsulfonylamino-C₁-C₄-alkoxy, C₃-C₁₂-heterocyclyl-C₁-C₄-alkoxy, C₆-C₁₂-aryloxy, C₃-C₁₂-heterocyclyloxy, C₁-C₆-alkylthio, halogenated C₁-C₆-alkylthio, C₁-C₆-alkylamino, (halogenated C₁-C₆-alkyl)amino, di-C₁-C₆-alkylamino (e.g. dimethylamino), di-(halogenated C₁-C₆-alkyl)amino, C₁-C₆-alkylcarbonylamino, (halogenated C₁-C₆-alkyl)carbonylamino, C₆-C₁₂-arylcarbonylamino, C₁-C₆-alkylsulfonylamino, (halogenated C₁-C₆-alkyl)sulfonylamino, C₆-C₁₂-arylsulfonylamino or optionally substituted C₃-C₁₂-heterocyclyl (e.g. 3-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-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).
- 25 Preferably, R¹ is C₁-C₆-alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, sec-butyl, n-butyl or n-pentyl), C₃-C₁₂-cycloalkyl-C₁-C₄-alkyl (e.g. cyclopropylmethyl, cyclopentylmethyl or cyclohexylmethyl), halogenated C₁-C₆-alkyl (e.g. 3-fluoroprop-1-yl, 3-chloroprop-1-yl or 3,3,3-trifluoroprop-1-yl), tri-(C₁-C₄-alkyl)-silyl-C₁-C₄-alkyl (e.g. trimethylsilylethyl), C₁-C₆-alkoxy-C₁-C₄-alkyl (e.g. ethoxyethyl), amino-C₁-C₄-alkyl, C₁-C₆-alkylamino-C₁-C₄-alkyl, di-C₁-C₆-alkylamino-C₁-C₄-alkyl, C₁-C₆-alkyloxycarbonylamino-C₁-C₄-alkyl, C₁-C₆-alkylaminocarbonylamino-C₁-C₄-alkyl, C₆-C₁₂-aryl-C₁-C₄-alkyl, C₃-C₁₂-cycloalkyl (e.g. cyclopropyl or cyclobutyl), C₂-C₆-alkenyl (e.g. prop-1,2-en-1-yl), optionally substituted C₆-C₁₂-aryl (e.g. phenyl), hydroxy, C₁-C₆-alkylamino, (halogenated C₁-C₆-alkyl)amino, di-C₁-C₆-alkylamino or optionally substituted C₃-C₁₂-heterocyclyl (e.g. 3-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-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).

In particular, R^1 is C_1 - C_6 -alkyl (e.g. ethyl or n-propyl), 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-methyl-1,3-diazol-4-yl, 3-oxetanyl, 1-methyl-pyrrol-3-yl).

5

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.

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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, 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.

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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.

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

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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 $-NR^8-CO$ -.

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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 $-NR^8$ -.

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A^2 is optionally substituted C_1 - C_4 -alkylene (e.g. 1,2-ethylene), 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, A² may be optionally substituted C₂-C₄-alkenylene or optionally substituted C₂-C₄-alkynylene. Preferably, A² is optionally substituted C₁-C₄-alkylene (e.g. 1,2-ethylene). More preferably, A² is C₁-C₄-alkylene (e.g. 1,2-ethylene). Alternatively, it is preferred that A² is optionally substituted C₆-C₁₂-arylene, in particular C₆-C₁₂-arylene selected from the group consisting of phen-1,4-ylene and phen-1,3-ylene, or optionally substituted C₆-C₁₂-heteroarylene, in particular C₆-C₁₂-heteroarylene selected from the group consisting of pyrid-2,5-ylene and pyrid-2,4-ylene. If A² is a bond, X¹ is preferably optionally substituted C₁-C₄-alkylene. Alternatively, if A² is a bond, X¹ is in particular optionally substituted C₂-C₄-alkenylene or optionally substituted C₂-C₄-alkynylene.

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In connection with A², substituted C₁-C₄-alkylene in particular includes C₁-C₄-alkylene substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl and cyano.

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In connection with A², substituted C₂-C₄-alkenylene or substituted C₂-C₄-alkynylene in particular includes C₂-C₄-alkenylene or C₂-C₄-alkynylene substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl and cyano.

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In connection with A², substituted C₆-C₁₂-arylene in particular includes C₆-C₁₂-arylene substituted with 1, 2 or 3 substituents selected from the group consisting of C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxycarbonyl, cyano, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylsulfonyl, amino, C₁-C₄-alkylamino, C₁-C₄-dialkylamino, C₆-C₁₂-arylamino and C₃-C₁₂-heterocyclyl (e.g., morpholino or piperidinyl).

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In connection with A², substituted C₆-C₁₂-heteroarylene in particular includes C₆-C₁₂-heteroarylene substituted with 1, 2 or 3 substituents selected from the group consisting of C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxycarbonyl, cyano, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylsulfonyl, amino, C₁-C₄-alkylamino, C₁-C₄-dialkylamino, C₆-C₁₂-arylamino and C₃-C₁₂-heterocyclyl (e.g., morpholino or piperidinyl).

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X¹ is -O-, -NR¹¹-, -S- or optionally substituted C₁-C₄-alkylene (e.g. -CH₂-, 1,2-ethylene or 1,3-propylene). In connection with X¹, substituted C₁-C₄-alkylene in particular includes C₁-C₄-alkylene substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl and cyano. Additionally, X¹ may be optionally substituted C₂-C₄-alkenylene or optionally substituted C₂-C₄-alkynylene (e.g. propynylene). In connection with X¹, substituted C₂-C₄-alkenylene or substituted C₂-C₄-alkynylene in particular includes C₂-C₄-alkenylene or C₂-C₄-alkynylene substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl and cyano. Preferably, X¹ is -O-, -NR¹¹-, -S-. More preferably, X¹ is -O-. Alternatively, it is pre-

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ferred if X^1 is optionally substituted C_1 - C_4 -alkylene (e.g. $-CH_2-$, 1,2-ethylene or 1,3-propylene).

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 $R^1-NH-C(O)-A^2-X^1-$.

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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 structural 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.

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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.

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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.

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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. $-NH-CH_2-C\equiv C-$), 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 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.

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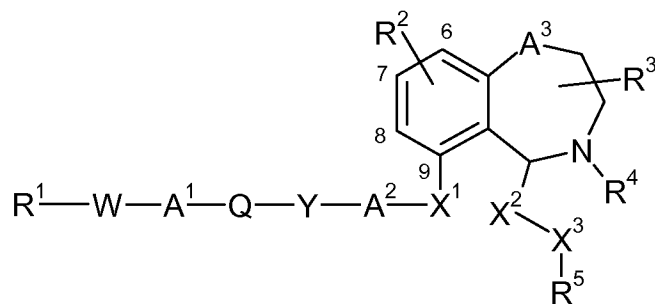
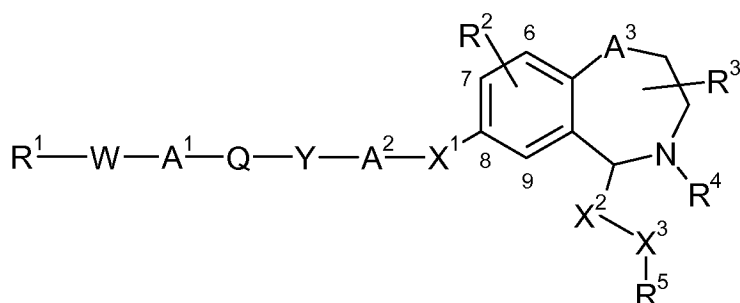
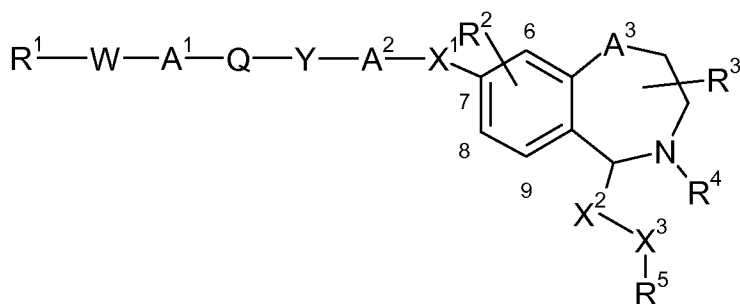
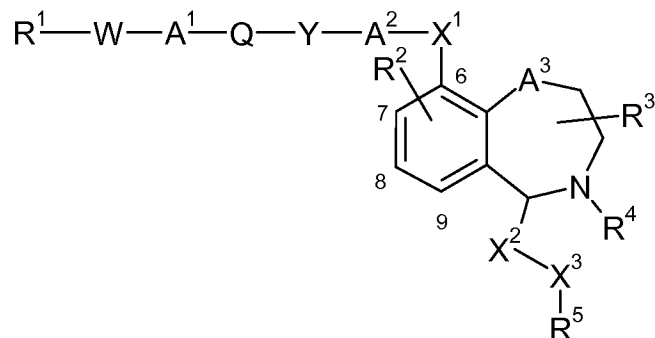
According to a further particular embodiment, $-Y-A^2-X^1-$ is $-C_1$ - C_4 -alkylene- (e.g. $-(CH_2)_2-$), with $-Y-A^2-X^1-$ preferably having 2 to 6, 2 to 5, 2 to 4 and especially 2 atoms in the main chain. If A is a heterocyclic ring, this embodiment of $-Y-A^2-X^1-$ is particularly suitable.

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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 $R^1-C(O)-Y-A^2-X^1$.

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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 6-, 7-, 8, or 9-position of the benzazepine skeleton:



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

Further particular examples include benzazepine derivatives of the above formulae wherein the radical R^1 -W- A^1 -Q-Y- A^2 - X^1 - is replaced by the radical -CN.

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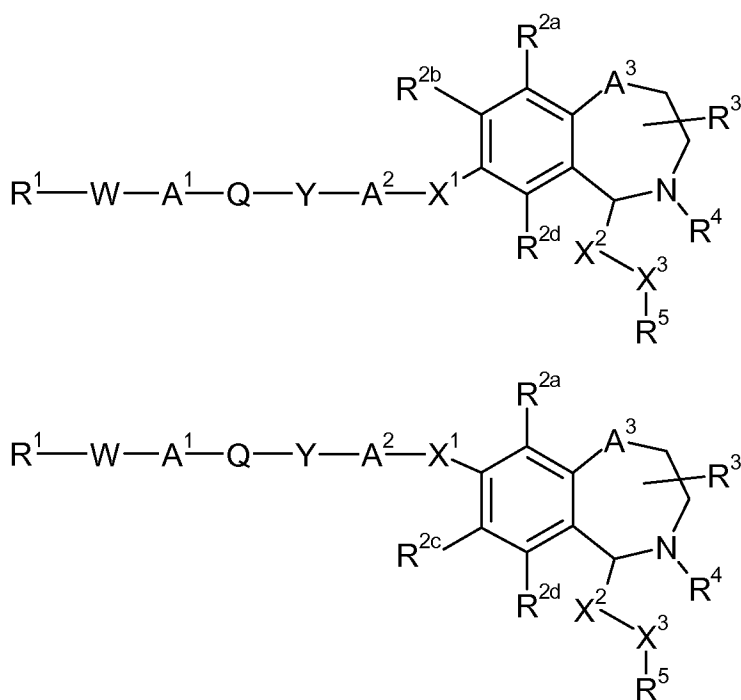
Benzazepine derivatives having the radical R^1 -W- A^1 -Q-Y- A^2 - X^1 - (or the radical -CN) in the 7-, 8-, 9-position are preferred.

Particularly preferred are benzazepine derivatives having the radical R^1 -W- A^1 -Q-Y- A^2 - X^1 - (or the radical -CN) in the 8-position.

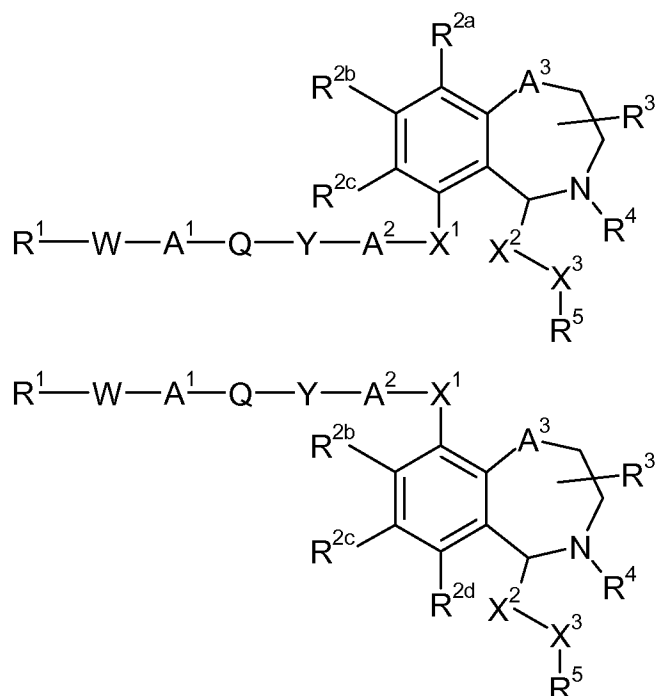
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In addition to the radical R^1 -W- A^1 -Q-Y- A^2 - X^1 - (or the radical -CN), the benzazepine derivatives of the invention may have one or more than one further substituent bound to the benzene ring. In these positions, the skeleton of the benzazepine derivatives 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 6-, 7-, 8- and/or 9-position, the benzazepine skeleton may be substituted with one or more than one radical R^2 . The benzazepine derivatives of the invention may therefore be represented by one of the following formulae:

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or by corresponding formulae wherein the radical $R^1-W-A^1-Q-Y-A^2-X^1$ is replaced by the radical $-CN$,

- 5 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 , R^4 , 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.

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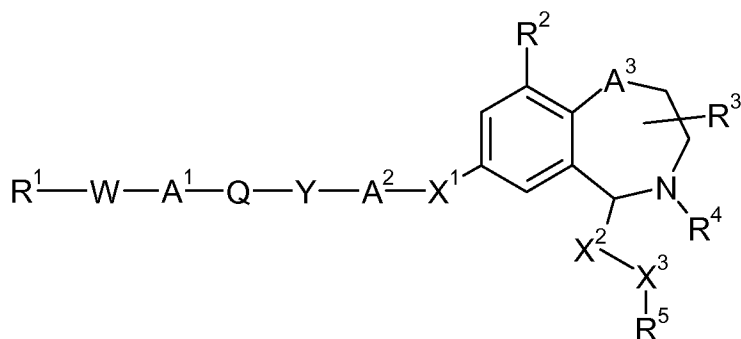
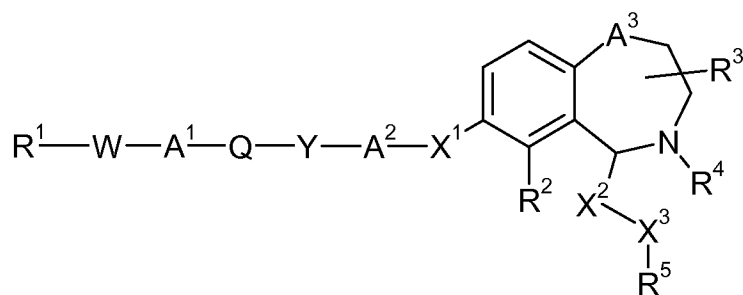
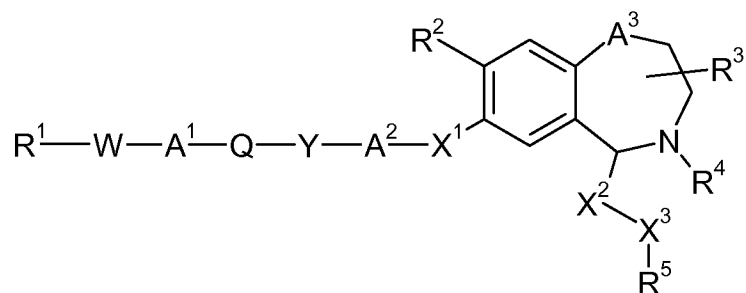
An optionally substituted 5- or 6-membered ring that is formed by two radicals R^2 together with the ring atoms of A to which they are bound is, for instance, a benzene ring.

- 20 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.

- 25 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).

- 5 According to a particular embodiment, the benzazepine derivatives of the invention have one of the following formulae:

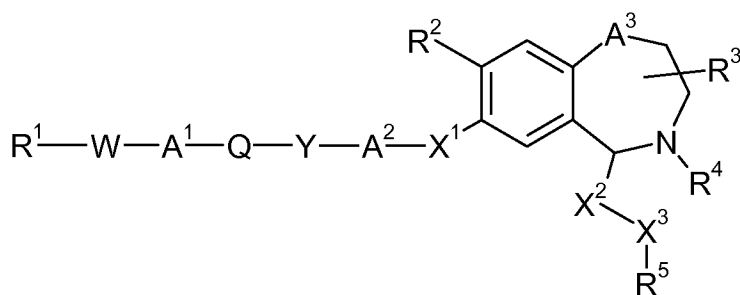


or a corresponding formula wherein the radical $R^1-W-A^1-Q-Y-A^2-X^1$ - is replaced by the radical $-CN$,

- 10 wherein R^1 , W , A^1 , Q , Y , A^2 , X^1 , R^2 , A^3 , R^3 , R^4 , X^2 , X^3 , R^5 are as defined herein.

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Particularly preferred are benzazepine derivatives of the following formula:



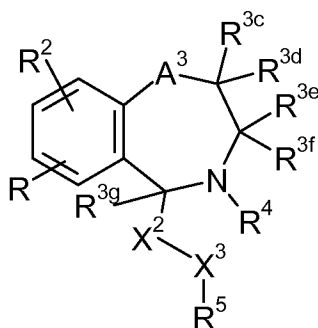
wherein R^1 , W , A^1 , Q , Y , A^2 , X^1 , R^2 , A^3 , R^3 , R^4 , X^2 , X^3 , R^5 are as defined herein, with R^2 preferably being halogen, in particular fluorine.

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A^3 is $-\text{CH}_2-$, $-\text{O}-$, $-\text{NR}^{16}-$, or $-\text{S}-$. If A^3 is $-\text{CH}_2-$, the compounds of formula (I) are referred to as 2,3,4,5-tetrahydro-1H-benzo[c]azepines. If A^3 is $-\text{O}-$, the compounds of formula (I) are referred to as 2,3,4,5-tetrahydro-1H-benzo[f][1,4]oxazepines. If A^3 is $-\text{NR}^{16}-$, the compounds of formula (I) are referred to as 2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepines. If A^3 is $-\text{S}-$, the compounds of formula (I) are referred to as 6,7,8,9-tetrahydro-5-thia-8-azabenzocycloheptenes. According to a particular embodiment, A^3 is $-\text{CH}_2-$, $-\text{O}-$ or $-\text{S}-$.

In 1-, 3-, 4- and/or 5-position, the benzazepine derivatives 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 benzazepine derivatives of the invention may therefore be represented by the following formula:

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wherein A^3 is $-\text{CR}^{3a}\text{R}^{3b}-$, $-\text{O}-$, $-\text{NR}^{16}-$, or $-\text{S}-$; R^{3a} , R^{3b} , R^{3c} , R^{3d} , R^{3e} , R^{3f} , R^{3g} independently have one of the meanings given for R^3 ; and R , R^2 , R^3 , R^4 , X^2 , X^3 , R^5 , R^{16} 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. In particular, R^3 is hydrogen.

25

R⁴ is hydrogen, C₁-C₆-alkyl (e.g. methyl, ethyl, n-propyl or isopropyl), C₃-C₁₂-cycloalkyl-C₁-C₄-alkyl (e.g. cyclopropylmethyl), halogenated C₁-C₄-alkyl (e.g. 2-fluoroethyl or 2,2,2-trifluoroethyl), hydroxy-C₁-C₄-alkyl, C₁-C₆-alkoxy-C₁-C₄-alkyl, amino-C₁-C₄-alkyl, C₆-C₁₂-aryl-C₁-C₄-alkyl, C₃-C₁₂-cycloalkyl (e.g. cyclopropyl), CH₂CN, -CHO, C₁-C₄-alkylcarbonyl (e.g. methylcarbonyl, ethylcarbonyl or isopropylcarbonyl), (halogenated C₁-C₄-alkyl)carbonyl (e.g. fluoromethylcarbonyl, difluoromethylcarbonyl, trifluoromethylcarbonyl, 1,1,1-trifluoroeth-2-ylcarbonyl or 1,1,1-trifluoroprop-3-ylcarbonyl), C₆-C₁₂-arylcarbonyl (e.g. phenylcarbonyl), C₁-C₄-alkoxycarbonyl (e.g. ethoxycarbonyl or tert-butyloxycarbonyl), C₆-C₁₂-aryloxycarbonyl (e.g. phenoxycarbonyl), C₁-C₆-alkylaminocarbonyl, C₂-C₆-alkenyl, -C(=NH)NH₂, -C(=NH)NHCN, C₁-C₆-alkylsulfonyl, C₆-C₁₂-arylsulfonyl, amino, -NO or C₃-C₁₂-heterocyclyl (e.g. 3-oxetanyl).

Preferably, R⁴ is hydrogen, C₁-C₆-alkyl (e.g. methyl, ethyl, n-propyl or isopropyl), C₃-C₁₂-cycloalkyl-C₁-C₄-alkyl (e.g. cyclopropylmethyl), halogenated C₁-C₄-alkyl (e.g. 2-fluoroethyl or 2,2,2-trifluoroethyl), amino-C₁-C₄-alkyl, C₆-C₁₂-aryl-C₁-C₄-alkyl, C₃-C₁₂-cycloalkyl (e.g. cyclopropyl), CH₂CN, C₁-C₄-alkylcarbonyl (e.g. methylcarbonyl or isopropylcarbonyl), (halogenated C₁-C₄-alkyl)carbonyl (e.g. fluoromethylcarbonyl, difluoromethylcarbonyl or trifluoromethylcarbonyl), C₆-C₁₂-arylcarbonyl (e.g. phenylcarbonyl), C₁-C₄-alkoxycarbonyl (e.g. ethoxycarbonyl or tert-butyloxycarbonyl), C₆-C₁₂-aryloxycarbonyl (e.g. phenoxycarbonyl), -C(=NH)NH₂, -C(=NH)NHCN, C₁-C₆-alkylsulfonyl, amino, -NO or C₃-C₁₂-heterocyclyl (e.g. 3-oxetanyl).

In particular, R⁴ is hydrogen, C₁-C₆-alkyl (e.g. methyl, ethyl or n-propyl), C₃-C₁₂-cycloalkyl (e.g. cyclopropyl) or C₃-C₁₂-cycloalkyl-C₁-C₄-alkyl (e.g. cyclopropylmethyl).

X² is -O-, -NR⁶-, -S-, >CR^{12a}R^{12b} or a bond. Preferably, X² is >CR^{12a}R^{12b}.

X³ is -O-, -NR⁷-, -S-, >CR^{13a}R^{13b} or a bond. Preferably, X³ is a bond.

Thus, it is preferred if X² is >CR^{12a}R^{12b} and X³ is a bond.

R^{12a} is hydrogen, optionally substituted C₁-C₆-alkyl, C₁-C₆-alkylamino-C₁-C₄-alkyl, di-C₁-C₆-alkylamino-C₁-C₄-alkyl, C₃-C₁₂-heterocyclyl-C₁-C₆-alkyl, optionally substituted C₆-C₁₂-aryl or hydroxy. Preferably, R^{12a} is hydrogen or C₁-C₆-alkyl.

R^{13a} is hydrogen, optionally substituted C₁-C₆-alkyl, C₁-C₆-alkylamino-C₁-C₄-alkyl, di-C₁-C₆-alkylamino-C₁-C₄-alkyl, C₃-C₁₂-heterocyclyl-C₁-C₆-alkyl, optionally substituted C₆-C₁₂-aryl or hydroxy. Preferably, R^{13a} is hydrogen or C₁-C₆-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.

- 5 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.

10

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 -
15 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 -
20 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.

- 25 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.
30

- 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.
35

- 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
40 group consisting of halogen, optionally substituted C_1 - C_6 -alkyl, halogenated C_1 - C_6 -alkyl,

CN, hydroxy, C₁-C₆-alkoxy, halogenated C₁-C₆-alkoxy, amino, C₁-C₆-alkylamino, di-C₁-C₆-alkylamino and C₃-C₁₂-heterocyclyl.

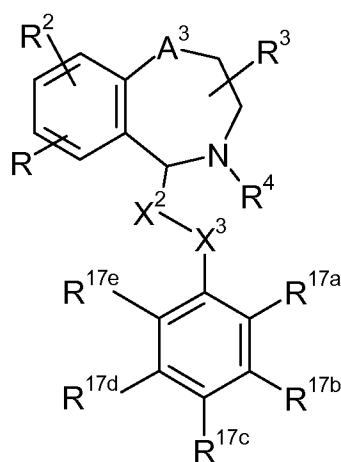
5 In connection with R⁵, substituted C₆-C₁₂-aryl in particular includes C₆-C₁₂-aryl, such as phenyl, substituted with 1, 2 or 3 substituents selected from the group consisting of halogen (e.g. F, Cl, Br), optionally substituted C₁-C₆-alkyl (e.g. methyl), halogenated C₁-C₆-alkyl (e.g. trifluoromethyl), CN, hydroxy, C₁-C₆-alkoxy (e.g. methoxy), halogenated C₁-C₆-alkoxy, amino, C₁-C₆-alkylamino, di-C₁-C₆-alkylamino and C₃-C₁₂-heterocyclyl.

10 In connection with R⁵, substituted C₃-C₁₂-heterocyclyl in particular includes C₃-C₁₂-heterocyclyl substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, optionally substituted C₁-C₆-alkyl, halogenated C₁-C₆-alkyl, CN, hydroxy, C₁-C₆-alkoxy, halogenated C₁-C₆-alkoxy, amino, C₁-C₆-alkylamino, di-C₁-C₆-alkylamino and C₃-C₁₂-heterocyclyl.

15 In connection with R⁵, C₃-C₁₂-heterocyclyl in particular is C₃-C₁₂-heteroaryl.

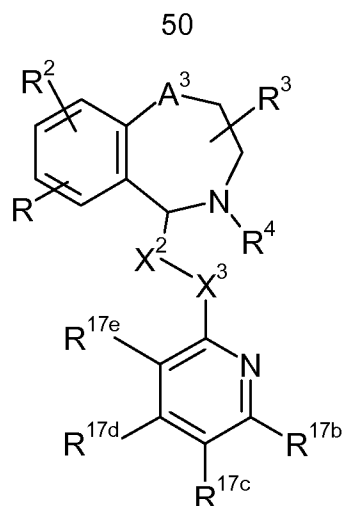
Preferably, R⁵ is optionally substituted C₆-C₁₂-aryl, in particular as in the benzazepine derivatives of the formula:

20



wherein R, R², A³, R³, R⁴, X², X³ are as defined herein, and R^{17a}, R^{17b}, R^{17c}, R^{17d}, R^{17e} independently are hydrogen, halogen (e.g. F, Cl or Br), optionally substituted C₁-C₆-alkyl (e.g. methyl), halogenated C₁-C₆-alkyl (e.g. trifluoromethyl),
 25 CN, hydroxy, C₁-C₆-alkoxy (e.g. methoxy), amino, C₁-C₆-alkylamino, di-C₁-C₆-alkylamino or C₃-C₁₂-heterocyclyl.

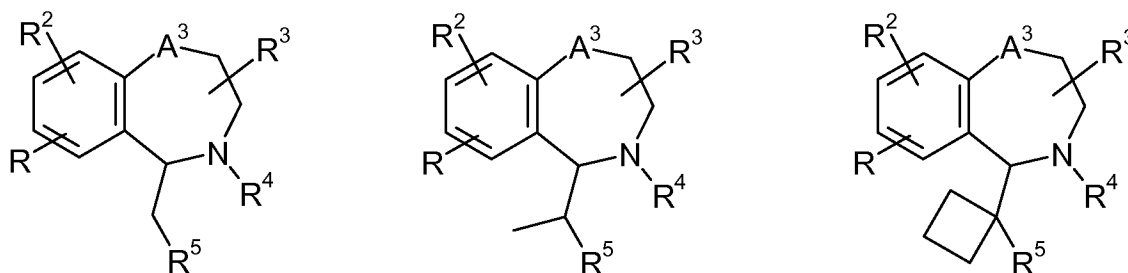
It is also preferred if R⁵ is optionally substituted C₆-C₁₂-heteroaryl, in particular as in the benzazepine derivatives of the formula:



wherein R, R², A³, R³, R⁴, X², X³ are as defined herein, and
 R^{17b}, R^{17c}, R^{17d}, R^{17e} independently are hydrogen, halogen (e.g. F, Cl or Br), optionally
 substituted C₁-C₆-alkyl (e.g. methyl), halogenated C₁-C₆-alkyl (e.g. trifluoromethyl), CN,
 5 hydroxy, C₁-C₆-alkoxy (e.g. methoxy), amino, C₁-C₆-alkylamino, di-C₁-C₆-alkylamino or C₃-
 C₁₂-heterocyclyl.

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

10



wherein R, R², A³, R³, R⁴, R⁵ are as defined herein, R⁵ preferably being optionally substi-
 tuted aryl and in particular optionally substituted phenyl as disclosed herein.

15

In connection with R⁵ or R^{17a}, R^{17b}, R^{17c}, R^{17d}, R^{17e}, substituted C₁-C₆-alkyl in particular
 includes C₁-C₆-alkyl, especially C₁-C₄-alkyl, substituted with 1, 2 or 3 substituents selected
 from the group consisting of hydroxy, C₁-C₆-alkoxy, amino, C₁-C₆-alkylamino, di-C₁-C₆-
 alkylamino and C₃-C₁₂-heterocyclyl (e.g. morpholinyl or piperidinyl).

20

According to a particular embodiment, R^{17a}, R^{17b}, R^{17d}, R^{17e} are hydrogen and R^{17c} is dif-
 ferent from hydrogen (para-mono-substitution).

According to a further particular embodiment, R^{17a}, R^{17c}, R^{17d}, R^{17e} are hydrogen and R^{17b}
 25 is different from hydrogen (meta-mono-substitution).

According to a further particular embodiment, R^{17b} , R^{17c} , R^{17d} , R^{17e} are hydrogen and R^{17a} is different from hydrogen (meta-ortho-substitution).

- 5 In connection with R^{17a} , R^{17b} , R^{17c} , R^{17d} , R^{17e} , C_3 - C_{12} -heterocyclyl in particular includes morpholinyl, imidazolyl and pyrazolyl.

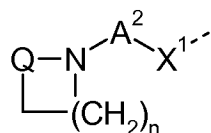
R^6 is hydrogen or C_1 - C_6 -alkyl. Preferably, R^6 is hydrogen.

- 10 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.

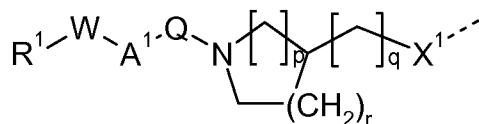
- 15 R^9 is hydrogen, C_1 - C_6 -alkyl (e.g. methyl or ethyl), C_3 - C_{12} -cycloalkyl (e.g. cyclopropyl), amino- C_1 - C_6 -alkyl, optionally substituted C_6 - C_{12} -aryl- C_1 - C_4 -alkyl or C_3 - C_{12} -heterocyclyl (e.g. 3-azetidiny). Preferably, R^9 is hydrogen or C_1 - C_6 -alkyl (e.g. methyl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

- 20 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:



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

- 30 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:

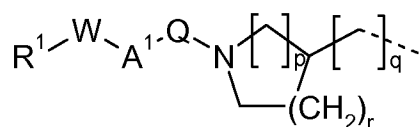


wherein R^1 , W, A^1 , Q and X^1 are as defined herein, p is 1 or 2, r is 0, 1 or 2 and q is 0, 1 or 2. In this particular embodiment, X^1 preferably is -O-. Particular combinations of p, r and q include p=1, r=0, q=1; and p=1, r=0, q=0. Alternatively, p is 0, r is 3 and q is 1, with X^1 preferably being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

5

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:

10



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.

15

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.

20

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.

25

R^{16} is hydrogen or C_1 - C_6 -alkyl. Preferably, R^{16} is hydrogen or C_1 - C_6 -alkyl (e.g. methyl).

Particular embodiments of benzazepine derivatives of the invention result if

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

30

R^1 is C_1 - C_6 -alkyl (e.g. ethyl or n-propyl), 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-methyl-1,3-diazol-4-yl, 3-oxetanyl, 1-methyl-pyrrol-3-yl);

W is a bond;

35

A^1 is a bond;

Q is -S(O)₂-;

- Y is -NR⁹- or a bond;
- A² is C₁-C₄-alkylene (e.g. 1,2-ethylene) or a bond;
- X¹ is -O- or optionally substituted C₁-C₄-alkylene (e.g. methylene, 1,2-ethylene or 1,3-propylene);
- 5 R² is hydrogen or halogen (e.g. fluorine);
- A³ is -CH₂-, -O-, -NR¹⁶, or -S-;
- R³ is hydrogen;
- R⁴ is hydrogen, C₁-C₆-alkyl (e.g. methyl, ethyl or n-propyl), C₃-C₁₂-cycloalkyl (e.g. cyclopropyl) or or C₃-C₁₂-cycloalkyl-C₁-C₄-alkyl (e.g. cyclopropylmethyl);
- 10 X² is >CR^{12a}R^{12b};
- X³ is a bond;
- R⁵ is optionally substituted phenyl (e.g. phenyl, 2-fluorophenyl, 2-chlorophenyl, 3-fluorophenyl, 3-chlorophenyl, 3-trifluoromethylphenyl, 4-fluorophenyl, 4-chlorophenyl) or optionally substituted pyridyl (e.g. 2-pyridyl);
- 15 R⁹ is hydrogen, or
- R⁹ is C₁-C₄-alkylene (e.g. methylene) that is bound to a carbon atom in X¹ and X¹ is C₁-C₄-alkylene (e.g. 1,2-ethylene);
- R^{12a} is hydrogen;
- R^{12b} is hydrogen; or
- 20 R^{12a}, R^{12b}
- together are C₁-C₄-alkylene (e.g. 1,3-propylene); and
- R¹⁶ is hydrogen or C₁-C₆-alkyl (e.g. methyl).

Further particular compounds of the present invention are the individual benzazepine derivatives of the formula (Id) as listed in the following tables 1 to 12 and physiologically tolerated salts thereof:

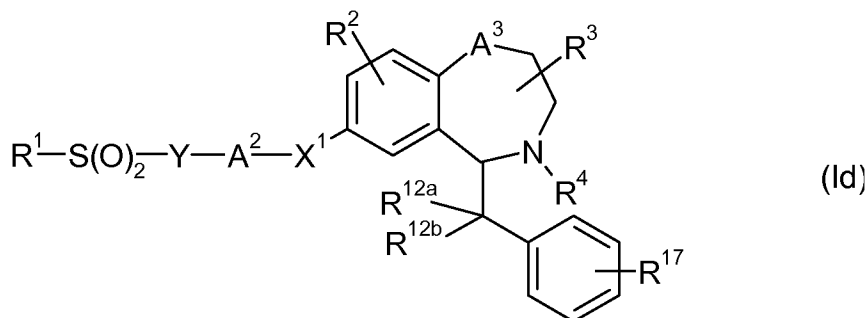


Table 1

Compounds of the formula (Id) wherein R^2 is hydrogen, R^3 is hydrogen, R^{17} is hydrogen and the combination of R^1 , $-Y-A^2-X^1-$, $>CR^{12a}R^{12b}$, A^3 , R^4 for a compound in each case corresponds to one line of Table A (A-1 to A-448).

5 Table 2

Compounds of the formula (Id) wherein R^2 is hydrogen, R^3 is hydrogen, R^{17} is 3-F and the combination of R^1 , $-Y-A^2-X^1-$, $>CR^{12a}R^{12b}$, A^3 , R^4 for a compound in each case corresponds to one line of Table A (A-1 to A-448).

10 Table 3

Compounds of the formula (Id) wherein R^2 is hydrogen, R^3 is hydrogen, R^{17} is 3-Cl and the combination of R^1 , $-Y-A^2-X^1-$, $>CR^{12a}R^{12b}$, A^3 , R^4 for a compound in each case corresponds to one line of Table A (A-1 to A-448).

15 Table 4

Compounds of the formula (Id) wherein R^2 is hydrogen, R^3 is hydrogen, R^{17} is 3-CF₃ and the combination of R^1 , $-Y-A^2-X^1-$, $>CR^{12a}R^{12b}$, A^3 , R^4 for a compound in each case corresponds to one line of Table A (A-1 to A-448).

20 Table 5

Compounds of the formula (Id) wherein R^2 is hydrogen, R^3 is hydrogen, R^{17} is 4-F and the combination of R^1 , $-Y-A^2-X^1-$, $>CR^{12a}R^{12b}$, A^3 , R^4 for a compound in each case corresponds to one line of Table A (A-1 to A-448).

25 Table 6

Compounds of the formula (Id) wherein R^2 is hydrogen, R^3 is hydrogen, R^{17} is 4-Cl and the combination of R^1 , $-Y-A^2-X^1-$, $>CR^{12a}R^{12b}$, A^3 , R^4 for a compound in each case corresponds to one line of Table A (A-1 to A-448).

30 Table 7

Compounds of the formula (Id) wherein R^2 is 7-F, R^3 is hydrogen, R^{17} is hydrogen and the combination of R^1 , $-Y-A^2-X^1-$, $>CR^{12a}R^{12b}$, A^3 , R^4 for a compound in each case corresponds to one line of Table A (A-1 to A-448).

35 Table 8

Compounds of the formula (Id) wherein R^2 is 7-F, R^3 is hydrogen, R^{17} is 3-F and the combination of R^1 , $-Y-A^2-X^1-$, $>CR^{12a}R^{12b}$, A^3 , R^4 for a compound in each case corresponds to one line of Table A (A-1 to A-448).

5 Table 9

Compounds of the formula (Id) wherein R^2 is 7-F, R^3 is hydrogen, R^{17} is 3-Cl and the combination of R^1 , $-Y-A^2-X^1-$, $>CR^{12a}R^{12b}$, A^3 , R^4 for a compound in each case corresponds to one line of Table A (A-1 to A-448).

10 Table 10

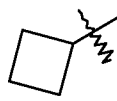
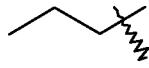
Compounds of the formula (Id) wherein R^2 is 7-F, R^3 is hydrogen, R^{17} is 3-CF₃ and the combination of R^1 , $-Y-A^2-X^1-$, $>CR^{12a}R^{12b}$, A^3 , R^4 for a compound in each case corresponds to one line of Table A (A-1 to A-448).

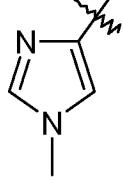
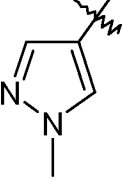
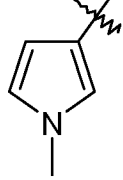
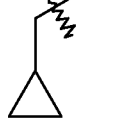
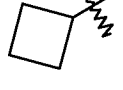
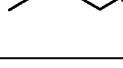
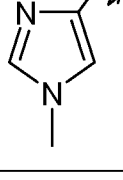
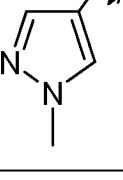
15 Table 11

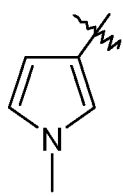
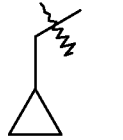
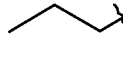
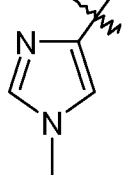
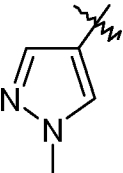
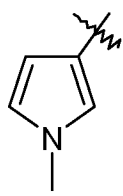
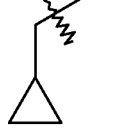
Compounds of the formula (Id) wherein R^2 is 7-F, R^3 is hydrogen, R^{17} is 4-F and the combination of R^1 , $-Y-A^2-X^1-$, $>CR^{12a}R^{12b}$, A^3 , R^4 for a compound in each case corresponds to one line of Table A (A-1 to A-448).

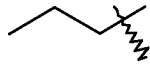
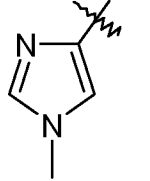
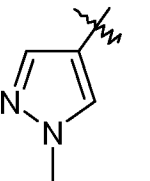
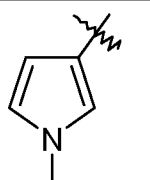
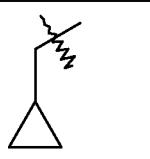
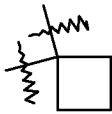
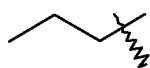
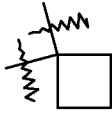
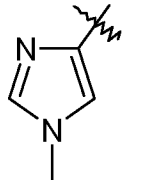
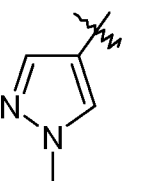
20 Table 12

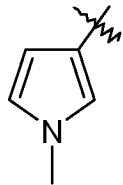
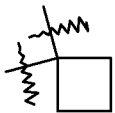
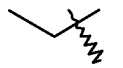
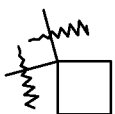
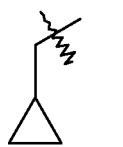
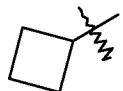
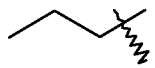
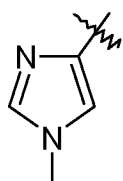
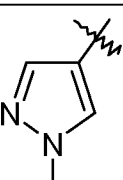
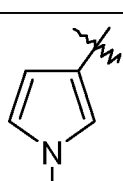
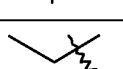
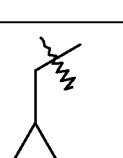
Compounds of the formula (Id) wherein R^2 is 7-F, R^3 is hydrogen, R^{17} is 4-Cl and the combination of R^1 , $-Y-A^2-X^1-$, $>CR^{12a}R^{12b}$, A^3 , R^4 for a compound in each case corresponds to one line of Table A (A-1 to A-448).

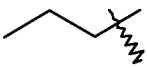
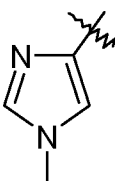
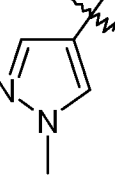
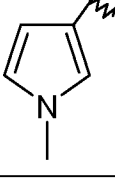
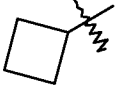
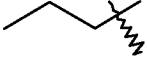
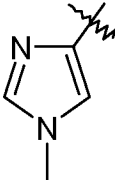
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	A^3	R^4
A-1.		$-NH-(CH_2)_3-$	$-CH_2-$	$-CH_2-$	$-H$
A-2.		$-NH-(CH_2)_3-$	$-CH_2-$	$-CH_2-$	$-H$
A-3.		$-NH-(CH_2)_3-$	$-CH_2-$	$-CH_2-$	$-H$

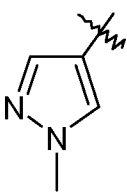
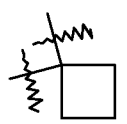
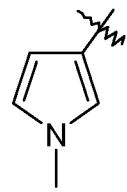
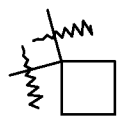
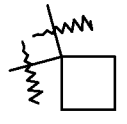
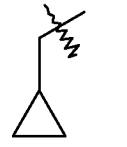
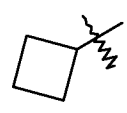
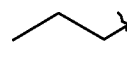
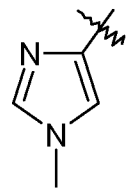
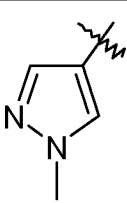
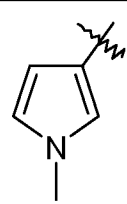
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-4.		-NH- (CH ₂) ₃ -	-CH ₂ -	-CH ₂ -	-H
A-5.		-NH- (CH ₂) ₃ -	-CH ₂ -	-CH ₂ -	-H
A-6.		-NH- (CH ₂) ₃ -	-CH ₂ -	-CH ₂ -	-H
A-7.		-NH- (CH ₂) ₃ -	-CH ₂ -	-CH ₂ -	-H
A-8.		-NH- (CH ₂) ₂ -O-	-CH ₂ -	-CH ₂ -	-H
A-9.		-NH- (CH ₂) ₂ -O-	-CH ₂ -	-CH ₂ -	-H
A-10.		-NH- (CH ₂) ₂ -O-	-CH ₂ -	-CH ₂ -	-H
A-11.		-NH- (CH ₂) ₂ -O-	-CH ₂ -	-CH ₂ -	-H
A-12.		-NH- (CH ₂) ₂ -O-	-CH ₂ -	-CH ₂ -	-H

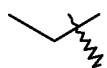
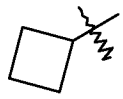
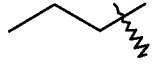
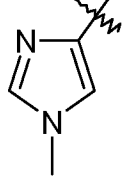
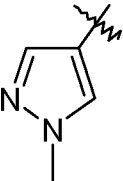
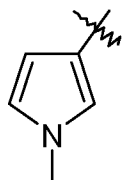
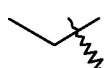
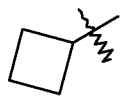
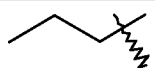
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-13.		-NH- (CH ₂) ₂ -O-	-CH ₂ -	-CH ₂ -	-H
A-14.		-NH- (CH ₂) ₂ -O-	-CH ₂ -	-CH ₂ -	-H
A-15.		-NH- (CH ₂) ₂ -	-CH ₂ -	-CH ₂ -	-H
A-16.		-NH- (CH ₂) ₂ -	-CH ₂ -	-CH ₂ -	-H
A-17.		-NH- (CH ₂) ₂ -	-CH ₂ -	-CH ₂ -	-H
A-18.		-NH- (CH ₂) ₂ -	-CH ₂ -	-CH ₂ -	-H
A-19.		-NH- (CH ₂) ₂ -	-CH ₂ -	-CH ₂ -	-H
A-20.		-NH- (CH ₂) ₂ -	-CH ₂ -	-CH ₂ -	-H
A-21.		-NH- (CH ₂) ₂ -	-CH ₂ -	-CH ₂ -	-H
A-22.		-NH-CH ₂ -	-CH ₂ -	-CH ₂ -	-H
A-23.		-NH-CH ₂ -	-CH ₂ -	-CH ₂ -	-H

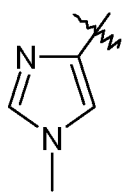
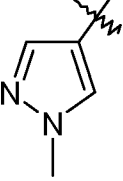
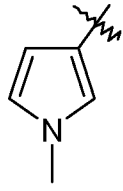
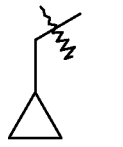
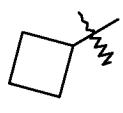
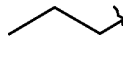
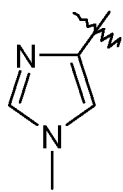
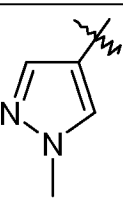
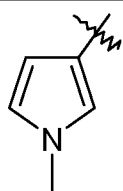
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	A^3	R^4
A-24.		$-NH-CH_2-$	$-CH_2-$	$-CH_2-$	$-H$
A-25.		$-NH-CH_2-$	$-CH_2-$	$-CH_2-$	$-H$
A-26.		$-NH-CH_2-$	$-CH_2-$	$-CH_2-$	$-H$
A-27.		$-NH-CH_2-$	$-CH_2-$	$-CH_2-$	$-H$
A-28.		$-NH-CH_2-$	$-CH_2-$	$-CH_2-$	$-H$
A-29.		$-NH-(CH_2)_3-$		$-CH_2-$	$-H$
A-30.		$-NH-(CH_2)_3-$		$-CH_2-$	$-H$
A-31.		$-NH-(CH_2)_3-$		$-CH_2-$	$-H$
A-32.		$-NH-(CH_2)_3-$		$-CH_2-$	$-H$
A-33.		$-NH-(CH_2)_3-$		$-CH_2-$	$-H$

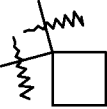
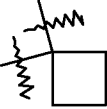
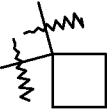
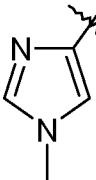
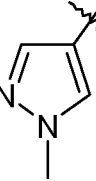
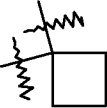
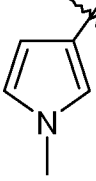
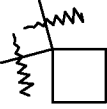
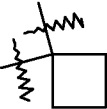
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	A^3	R^4
A-34.		$-NH-(CH_2)_3-$		$-CH_2-$	$-H$
A-35.		$-NH-(CH_2)_3-$		$-CH_2-$	$-H$
A-36.		$-NH-(CH_2)_2-O-$		$-CH_2-$	$-H$
A-37.		$-NH-(CH_2)_2-O-$		$-CH_2-$	$-H$
A-38.		$-NH-(CH_2)_2-O-$		$-CH_2-$	$-H$
A-39.		$-NH-(CH_2)_2-O-$		$-CH_2-$	$-H$
A-40.		$-NH-(CH_2)_2-O-$		$-CH_2-$	$-H$
A-41.		$-NH-(CH_2)_2-O-$		$-CH_2-$	$-H$
A-42.		$-NH-(CH_2)_2-O-$		$-CH_2-$	$-H$
A-43.		$-NH-(CH_2)_2-$		$-CH_2-$	$-H$

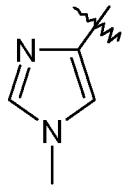
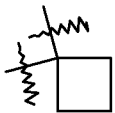
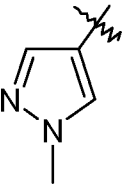
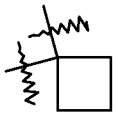
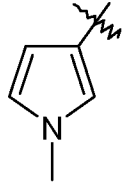
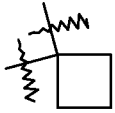
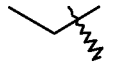
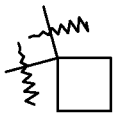
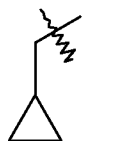
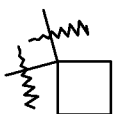
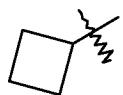
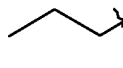
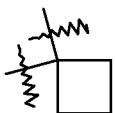
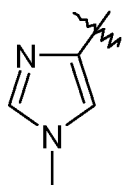
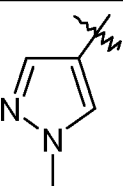
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	A^3	R^4
A-44.		$-NH-(CH_2)_2-$		$-CH_2-$	$-H$
A-45.		$-NH-(CH_2)_2-$		$-CH_2-$	$-H$
A-46.		$-NH-(CH_2)_2-$		$-CH_2-$	$-H$
A-47.		$-NH-(CH_2)_2-$		$-CH_2-$	$-H$
A-48.		$-NH-(CH_2)_2-$		$-CH_2-$	$-H$
A-49.		$-NH-(CH_2)_2-$		$-CH_2-$	$-H$
A-50.		$-NH-CH_2-$		$-CH_2-$	$-H$
A-51.		$-NH-CH_2-$		$-CH_2-$	$-H$
A-52.		$-NH-CH_2-$		$-CH_2-$	$-H$
A-53.		$-NH-CH_2-$		$-CH_2-$	$-H$

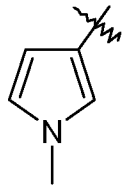
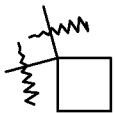
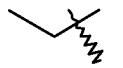
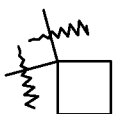
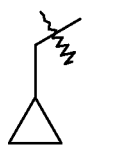
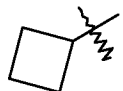
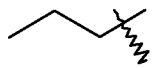
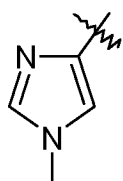
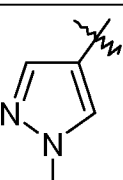
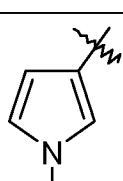
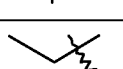
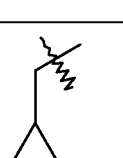
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-54.		-NH-CH ₂ -		-CH ₂ -	-H
A-55.		-NH-CH ₂ -		-CH ₂ -	-H
A-56.		-NH-CH ₂ -		-CH ₂ -	-H
A-57.		-NH-(CH ₂) ₃ -	-CH ₂ -	-CH ₂ -	-CH ₃
A-58.		-NH-(CH ₂) ₃ -	-CH ₂ -	-CH ₂ -	-CH ₃
A-59.		-NH-(CH ₂) ₃ -	-CH ₂ -	-CH ₂ -	-CH ₃
A-60.		-NH-(CH ₂) ₃ -	-CH ₂ -	-CH ₂ -	-CH ₃
A-61.		-NH-(CH ₂) ₃ -	-CH ₂ -	-CH ₂ -	-CH ₃
A-62.		-NH-(CH ₂) ₃ -	-CH ₂ -	-CH ₂ -	-CH ₃

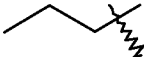
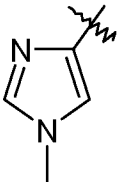
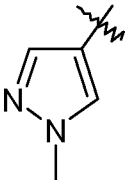
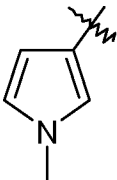
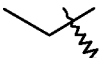
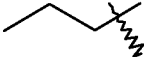
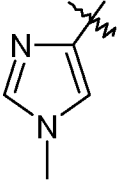
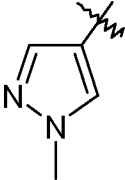
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	A^3	R^4
A-63.		$-NH-(CH_2)_3-$	$-CH_2-$	$-CH_2-$	$-CH_3$
A-64.		$-NH-(CH_2)_2-O-$	$-CH_2-$	$-CH_2-$	$-CH_3$
A-65.		$-NH-(CH_2)_2-O-$	$-CH_2-$	$-CH_2-$	$-CH_3$
A-66.		$-NH-(CH_2)_2-O-$	$-CH_2-$	$-CH_2-$	$-CH_3$
A-67.		$-NH-(CH_2)_2-O-$	$-CH_2-$	$-CH_2-$	$-CH_3$
A-68.		$-NH-(CH_2)_2-O-$	$-CH_2-$	$-CH_2-$	$-CH_3$
A-69.		$-NH-(CH_2)_2-O-$	$-CH_2-$	$-CH_2-$	$-CH_3$
A-70.		$-NH-(CH_2)_2-O-$	$-CH_2-$	$-CH_2-$	$-CH_3$
A-71.		$-NH-(CH_2)_2-$	$-CH_2-$	$-CH_2-$	$-CH_3$
A-72.		$-NH-(CH_2)_2-$	$-CH_2-$	$-CH_2-$	$-CH_3$
A-73.		$-NH-(CH_2)_2-$	$-CH_2-$	$-CH_2-$	$-CH_3$

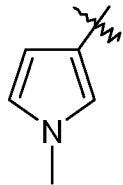
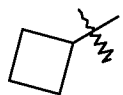
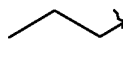
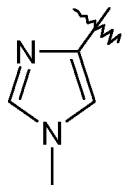
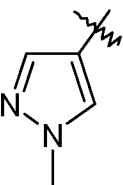
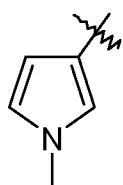
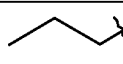
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-74.		-NH-(CH ₂) ₂ -	-CH ₂ -	-CH ₂ -	-CH ₃
A-75.		-NH-(CH ₂) ₂ -	-CH ₂ -	-CH ₂ -	-CH ₃
A-76.		-NH-(CH ₂) ₂ -	-CH ₂ -	-CH ₂ -	-CH ₃
A-77.		-NH-(CH ₂) ₂ -	-CH ₂ -	-CH ₂ -	-CH ₃
A-78.		-NH-CH ₂ -	-CH ₂ -	-CH ₂ -	-CH ₃
A-79.		-NH-CH ₂ -	-CH ₂ -	-CH ₂ -	-CH ₃
A-80.		-NH-CH ₂ -	-CH ₂ -	-CH ₂ -	-CH ₃
A-81.		-NH-CH ₂ -	-CH ₂ -	-CH ₂ -	-CH ₃
A-82.		-NH-CH ₂ -	-CH ₂ -	-CH ₂ -	-CH ₃
A-83.		-NH-CH ₂ -	-CH ₂ -	-CH ₂ -	-CH ₃

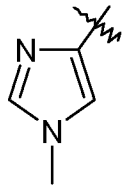
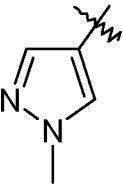
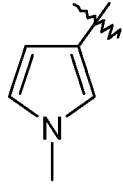
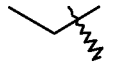
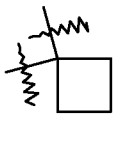
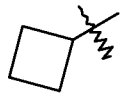
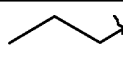
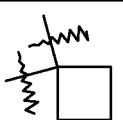
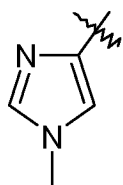
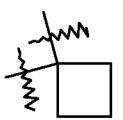
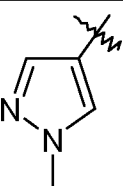
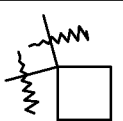
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	A^3	R^4
A-84.		$-NH-CH_2-$	$-CH_2-$	$-CH_2-$	$-CH_3$
A-85.		$-NH-(CH_2)_3-$		$-CH_2-$	$-CH_3$
A-86.		$-NH-(CH_2)_3-$		$-CH_2-$	$-CH_3$
A-87.		$-NH-(CH_2)_3-$		$-CH_2-$	$-CH_3$
A-88.		$-NH-(CH_2)_3-$		$-CH_2-$	$-CH_3$
A-89.		$-NH-(CH_2)_3-$		$-CH_2-$	$-CH_3$
A-90.		$-NH-(CH_2)_3-$		$-CH_2-$	$-CH_3$
A-91.		$-NH-(CH_2)_3-$		$-CH_2-$	$-CH_3$
A-92.		$-NH-(CH_2)_2-O-$		$-CH_2-$	$-CH_3$
A-93.		$-NH-(CH_2)_2-O-$		$-CH_2-$	$-CH_3$
A-94.		$-NH-(CH_2)_2-O-$		$-CH_2-$	$-CH_3$

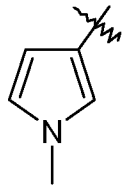
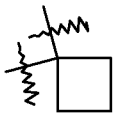
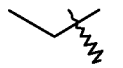
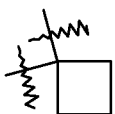
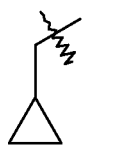
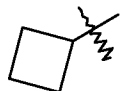
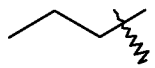
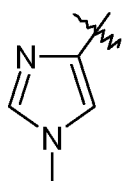
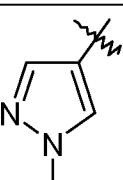
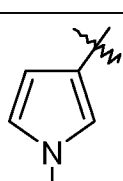
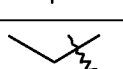
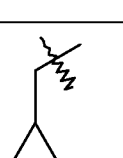
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-95.		-NH-(CH ₂) ₂ -O-		-CH ₂ -	-CH ₃
A-96.		-NH-(CH ₂) ₂ -O-		-CH ₂ -	-CH ₃
A-97.		-NH-(CH ₂) ₂ -O-		-CH ₂ -	-CH ₃
A-98.		-NH-(CH ₂) ₂ -O-		-CH ₂ -	-CH ₃
A-99.		-NH-(CH ₂) ₂ -		-CH ₂ -	-CH ₃
A-100.		-NH-(CH ₂) ₂ -		-CH ₂ -	-CH ₃
A-101.		-NH-(CH ₂) ₂ -		-CH ₂ -	-CH ₃
A-102.		-NH-(CH ₂) ₂ -		-CH ₂ -	-CH ₃
A-103.		-NH-(CH ₂) ₂ -		-CH ₂ -	-CH ₃

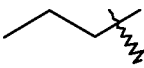
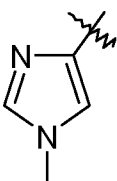
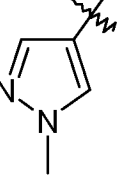
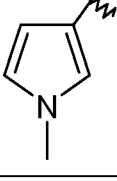
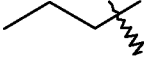
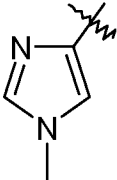
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	A^3	R^4
A-104.		$-NH-(CH_2)_2-$		$-CH_2-$	$-CH_3$
A-105.		$-NH-(CH_2)_2-$		$-CH_2-$	$-CH_3$
A-106.		$-NH-CH_2-$		$-CH_2-$	$-CH_3$
A-107.		$-NH-CH_2-$		$-CH_2-$	$-CH_3$
A-108.		$-NH-CH_2-$		$-CH_2-$	$-CH_3$
A-109.		$-NH-CH_2-$		$-CH_2-$	$-CH_3$
A-110.		$-NH-CH_2-$		$-CH_2-$	$-CH_3$
A-111.		$-NH-CH_2-$		$-CH_2-$	$-CH_3$
A-112.		$-NH-CH_2-$		$-CH_2-$	$-CH_3$
A-113.		$-NH-(CH_2)_3-$	$-CH_2-$	$-CH_2-$	$-CH_2CH_3$

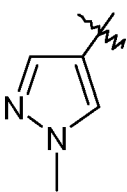
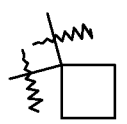
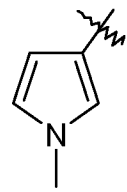
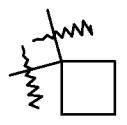
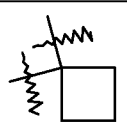
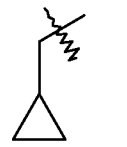
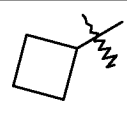
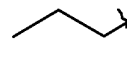
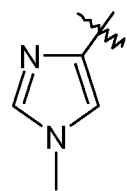
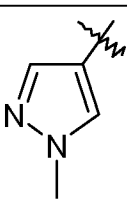
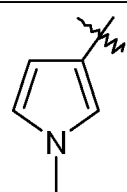
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-114.		-NH-(CH ₂) ₃ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₃
A-115.		-NH-(CH ₂) ₃ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₃
A-116.		-NH-(CH ₂) ₃ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₃
A-117.		-NH-(CH ₂) ₃ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₃
A-118.		-NH-(CH ₂) ₃ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₃
A-119.		-NH-(CH ₂) ₃ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₃
A-120.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₃
A-121.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₃
A-122.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₃
A-123.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₃
A-124.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₃

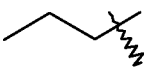
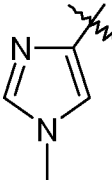
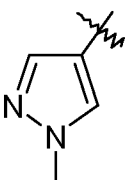
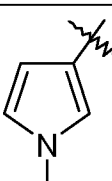
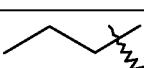
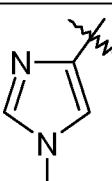
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-125.		-NH- (CH ₂) ₂ -O-	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₃
A-126.		-NH- (CH ₂) ₂ -O-	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₃
A-127.		-NH- (CH ₂) ₂ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₃
A-128.		-NH- (CH ₂) ₂ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₃
A-129.		-NH- (CH ₂) ₂ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₃
A-130.		-NH- (CH ₂) ₂ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₃
A-131.		-NH- (CH ₂) ₂ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₃
A-132.		-NH- (CH ₂) ₂ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₃
A-133.		-NH- (CH ₂) ₂ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₃
A-134.		-NH-CH ₂ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₃
A-135.		-NH-CH ₂ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₃
A-136.		-NH-CH ₂ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₃

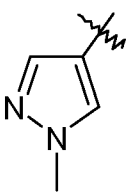
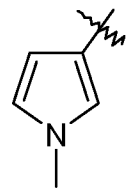
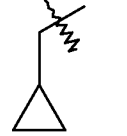
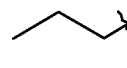
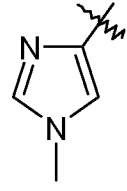
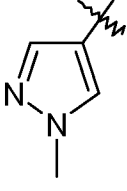
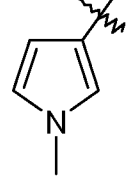
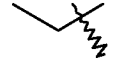
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-137.		-NH-CH ₂ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₃
A-138.		-NH-CH ₂ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₃
A-139.		-NH-CH ₂ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₃
A-140.		-NH-CH ₂ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₃
A-141.		-NH-(CH ₂) ₃ -		-CH ₂ -	-CH ₂ CH ₃
A-142.		-NH-(CH ₂) ₃ -		-CH ₂ -	-CH ₂ CH ₃
A-143.		-NH-(CH ₂) ₃ -		-CH ₂ -	-CH ₂ CH ₃
A-144.		-NH-(CH ₂) ₃ -		-CH ₂ -	-CH ₂ CH ₃
A-145.		-NH-(CH ₂) ₃ -		-CH ₂ -	-CH ₂ CH ₃

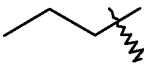
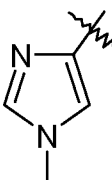
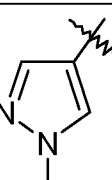
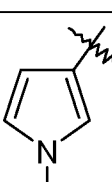
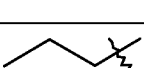
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-146.		-NH-(CH ₂) ₃ -		-CH ₂ -	-CH ₂ CH ₃
A-147.		-NH-(CH ₂) ₃ -		-CH ₂ -	-CH ₂ CH ₃
A-148.		-NH-(CH ₂) ₂ -O-		-CH ₂ -	-CH ₂ CH ₃
A-149.		-NH-(CH ₂) ₂ -O-		-CH ₂ -	-CH ₂ CH ₃
A-150.		-NH-(CH ₂) ₂ -O-		-CH ₂ -	-CH ₂ CH ₃
A-151.		-NH-(CH ₂) ₂ -O-		-CH ₂ -	-CH ₂ CH ₃
A-152.		-NH-(CH ₂) ₂ -O-		-CH ₂ -	-CH ₂ CH ₃
A-153.		-NH-(CH ₂) ₂ -O-		-CH ₂ -	-CH ₂ CH ₃
A-154.		-NH-(CH ₂) ₂ -O-		-CH ₂ -	-CH ₂ CH ₃
A-155.		-NH-(CH ₂) ₂ -		-CH ₂ -	-CH ₂ CH ₃

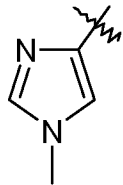
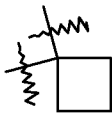
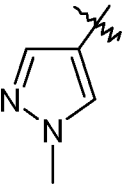
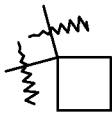
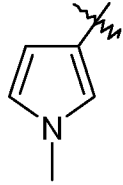
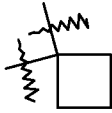
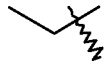
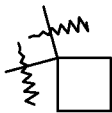
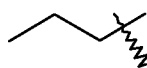
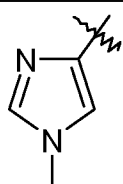
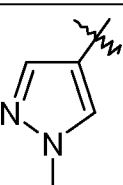
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	A^3	R^4
A-156.		$-NH-(CH_2)_2-$		$-CH_2-$	$-CH_2CH_3$
A-157.		$-NH-(CH_2)_2-$		$-CH_2-$	$-CH_2CH_3$
A-158.		$-NH-(CH_2)_2-$		$-CH_2-$	$-CH_2CH_3$
A-159.		$-NH-(CH_2)_2-$		$-CH_2-$	$-CH_2CH_3$
A-160.		$-NH-(CH_2)_2-$		$-CH_2-$	$-CH_2CH_3$
A-161.		$-NH-(CH_2)_2-$		$-CH_2-$	$-CH_2CH_3$
A-162.		$-NH-CH_2-$		$-CH_2-$	$-CH_2CH_3$
A-163.		$-NH-CH_2-$		$-CH_2-$	$-CH_2CH_3$
A-164.		$-NH-CH_2-$		$-CH_2-$	$-CH_2CH_3$
A-165.		$-NH-CH_2-$		$-CH_2-$	$-CH_2CH_3$

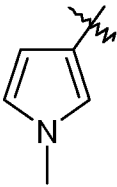
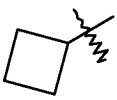
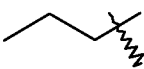
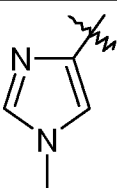
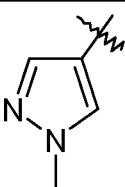
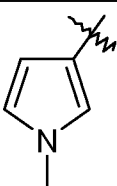
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-166.		-NH-CH ₂ -		-CH ₂ -	-CH ₂ CH ₃
A-167.		-NH-CH ₂ -		-CH ₂ -	-CH ₂ CH ₃
A-168.		-NH-CH ₂ -		-CH ₂ -	-CH ₂ CH ₃
A-169.		-NH-(CH ₂) ₃ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-170.		-NH-(CH ₂) ₃ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-171.		-NH-(CH ₂) ₃ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-172.		-NH-(CH ₂) ₃ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-173.		-NH-(CH ₂) ₃ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-174.		-NH-(CH ₂) ₃ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-175.		-NH-(CH ₂) ₃ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₂ CH ₃

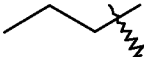
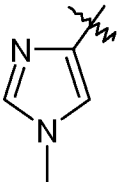
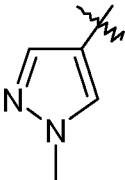
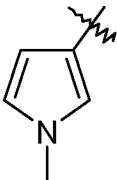
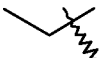
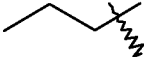
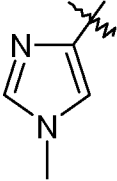
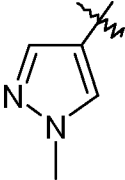
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-176.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-177.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-178.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-179.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-180.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-181.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-182.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-183.		-NH-(CH ₂) ₂ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-184.		-NH-(CH ₂) ₂ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-185.		-NH-(CH ₂) ₂ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-186.		-NH-(CH ₂) ₂ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₂ CH ₃

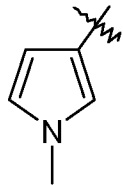
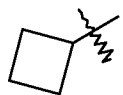
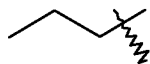
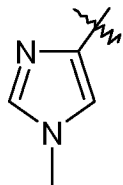
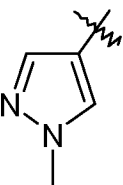
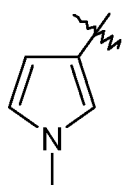
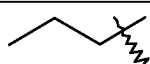
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-187.		-NH-(CH ₂) ₂ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₂ CH ₃ - CH ₂ CH ₃
A-188.		-NH-(CH ₂) ₂ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-189.		-NH-(CH ₂) ₂ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-190.		-NH-CH ₂ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-191.		-NH-CH ₂ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-192.		-NH-CH ₂ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-193.		-NH-CH ₂ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-194.		-NH-CH ₂ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-195.		-NH-CH ₂ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-196.		-NH-CH ₂ -	-CH ₂ -	-CH ₂ -	-CH ₂ CH ₂ CH ₃

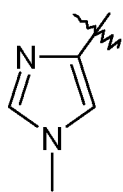
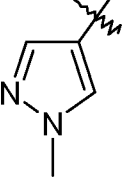
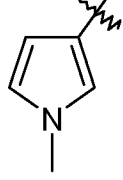
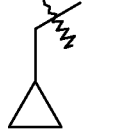
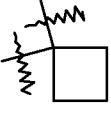
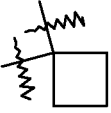
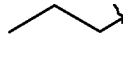
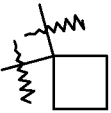
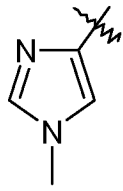
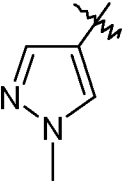
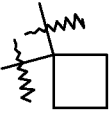
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-197.		-NH-(CH ₂) ₃ -		-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-198.		-NH-(CH ₂) ₃ -		-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-199.		-NH-(CH ₂) ₃ -		-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-200.		-NH-(CH ₂) ₃ -		-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-201.		-NH-(CH ₂) ₃ -		-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-202.		-NH-(CH ₂) ₃ -		-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-203.		-NH-(CH ₂) ₃ -		-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-204.		-NH-(CH ₂) ₂ -O-		-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-205.		-NH-(CH ₂) ₂ -O-		-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-206.		-NH-(CH ₂) ₂ -O-		-CH ₂ -	-CH ₂ CH ₂ CH ₃

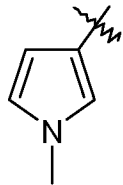
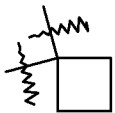
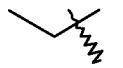
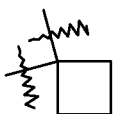
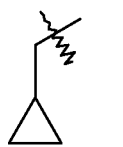
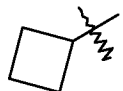
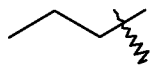
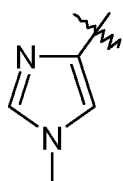
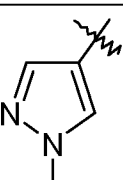
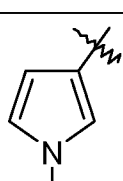
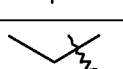
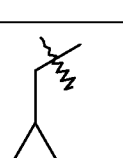
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-207.		-NH-(CH ₂) ₂ -O-		-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-208.		-NH-(CH ₂) ₂ -O-		-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-209.		-NH-(CH ₂) ₂ -O-		-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-210.		-NH-(CH ₂) ₂ -O-		-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-211.		-NH-(CH ₂) ₂ -		-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-212.		-NH-(CH ₂) ₂ -		-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-213.		-NH-(CH ₂) ₂ -		-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-214.		-NH-(CH ₂) ₂ -		-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-215.		-NH-(CH ₂) ₂ -		-CH ₂ -	-CH ₂ CH ₂ CH ₃

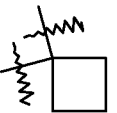
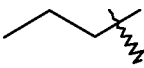
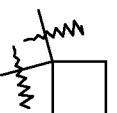
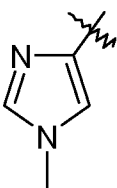
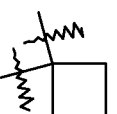
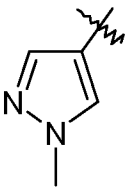
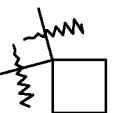
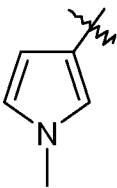
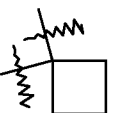
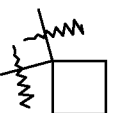
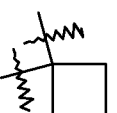
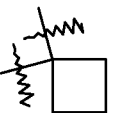
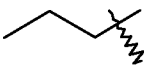
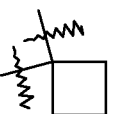
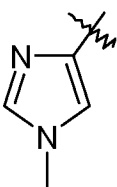
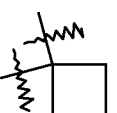
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-216.		-NH-(CH ₂) ₂ -		-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-217.		-NH-(CH ₂) ₂ -		-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-218.		-NH-CH ₂ -		-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-219.		-NH-CH ₂ -		-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-220.		-NH-CH ₂ -		-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-221.		-NH-CH ₂ -		-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-222.		-NH-CH ₂ -		-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-223.		-NH-CH ₂ -		-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-224.		-NH-CH ₂ -		-CH ₂ -	-CH ₂ CH ₂ CH ₃
A-225.		-NH-(CH ₂) ₃ -	-CH ₂ -	-O-	-H

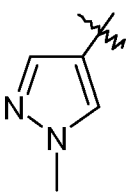
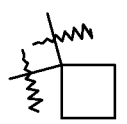
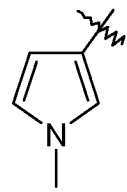
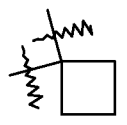
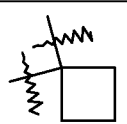
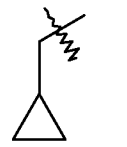
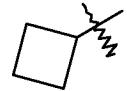
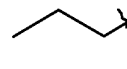
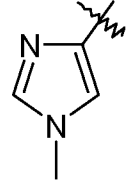
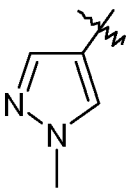
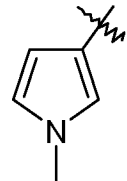
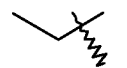
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-226.		-NH-(CH ₂) ₃ -	-CH ₂ -	-O-	-H
A-227.		-NH-(CH ₂) ₃ -	-CH ₂ -	-O-	-H
A-228.		-NH-(CH ₂) ₃ -	-CH ₂ -	-O-	-H
A-229.		-NH-(CH ₂) ₃ -	-CH ₂ -	-O-	-H
A-230.		-NH-(CH ₂) ₃ -	-CH ₂ -	-O-	-H
A-231.		-NH-(CH ₂) ₃ -	-CH ₂ -	-O-	-H
A-232.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-O-	-H
A-233.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-O-	-H
A-234.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-O-	-H
A-235.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-O-	-H
A-236.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-O-	-H

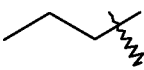
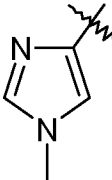
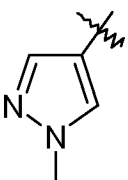
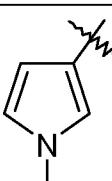
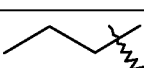
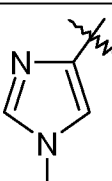
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-237.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-O-	-H
A-238.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-O-	-H
A-239.		-NH-(CH ₂) ₂ -	-CH ₂ -	-O-	-H
A-240.		-NH-(CH ₂) ₂ -	-CH ₂ -	-O-	-H
A-241.		-NH-(CH ₂) ₂ -	-CH ₂ -	-O-	-H
A-242.		-NH-(CH ₂) ₂ -	-CH ₂ -	-O-	-H
A-243.		-NH-(CH ₂) ₂ -	-CH ₂ -	-O-	-H
A-244.		-NH-(CH ₂) ₂ -	-CH ₂ -	-O-	-H
A-245.		-NH-(CH ₂) ₂ -	-CH ₂ -	-O-	-H
A-246.		-NH-CH ₂ -	-CH ₂ -	-O-	-H
A-247.		-NH-CH ₂ -	-CH ₂ -	-O-	-H
A-248.		-NH-CH ₂ -	-CH ₂ -	-O-	-H

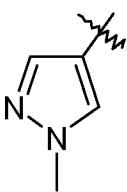
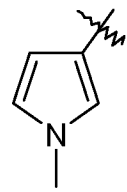
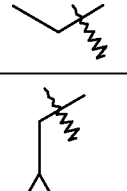
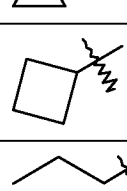
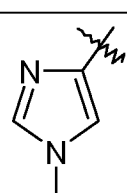
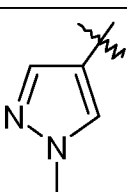
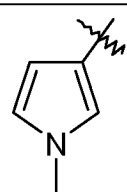
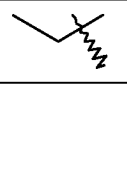
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-249.		-NH-CH ₂ -	-CH ₂ -	-O-	-H
A-250.		-NH-CH ₂ -	-CH ₂ -	-O-	-H
A-251.		-NH-CH ₂ -	-CH ₂ -	-O-	-H
A-252.		-NH-CH ₂ -	-CH ₂ -	-O-	-H
A-253.		-NH-(CH ₂) ₃ -		-O-	-H
A-254.		-NH-(CH ₂) ₃ -		-O-	-H
A-255.		-NH-(CH ₂) ₃ -		-O-	-H
A-256.		-NH-(CH ₂) ₃ -		-O-	-H
A-257.		-NH-(CH ₂) ₃ -		-O-	-H

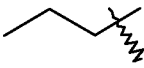
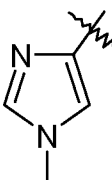
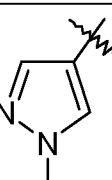
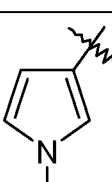
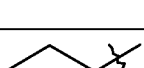
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-258.		-NH-(CH ₂) ₃ -		-O-	-H
A-259.		-NH-(CH ₂) ₃ -		-O-	-H
A-260.		-NH-(CH ₂) ₂ -O-		-O-	-H
A-261.		-NH-(CH ₂) ₂ -O-		-O-	-H
A-262.		-NH-(CH ₂) ₂ -O-		-O-	-H
A-263.		-NH-(CH ₂) ₂ -O-		-O-	-H
A-264.		-NH-(CH ₂) ₂ -O-		-O-	-H
A-265.		-NH-(CH ₂) ₂ -O-		-O-	-H
A-266.		-NH-(CH ₂) ₂ -O-		-O-	-H
A-267.		-NH-(CH ₂) ₂ -		-O-	-H

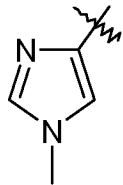
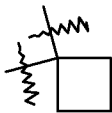
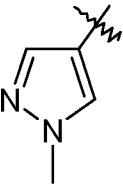
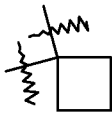
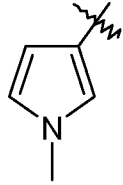
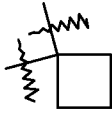
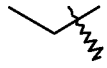
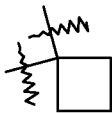
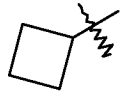
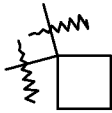
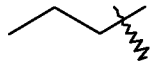
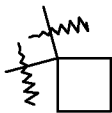
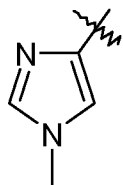
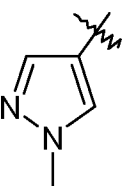
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	A^3	R^4
A-268.		$-NH-(CH_2)_2-$		$-O-$	$-H$
A-269.		$-NH-(CH_2)_2-$		$-O-$	$-H$
A-270.		$-NH-(CH_2)_2-$		$-O-$	$-H$
A-271.		$-NH-(CH_2)_2-$		$-O-$	$-H$
A-272.		$-NH-(CH_2)_2-$		$-O-$	$-H$
A-273.		$-NH-(CH_2)_2-$		$-O-$	$-H$
A-274.		$-NH-CH_2-$		$-O-$	$-H$
A-275.		$-NH-CH_2-$		$-O-$	$-H$
A-276.		$-NH-CH_2-$		$-O-$	$-H$
A-277.		$-NH-CH_2-$		$-O-$	$-H$

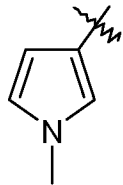
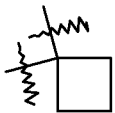
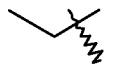
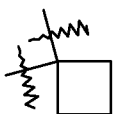
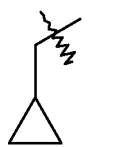
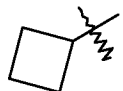
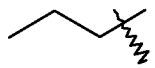
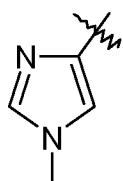
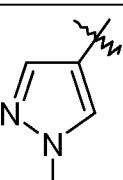
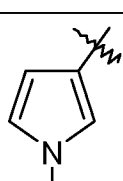
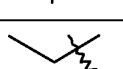
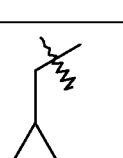
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-278.		-NH-CH ₂ -		-O-	-H
A-279.		-NH-CH ₂ -		-O-	-H
A-280.		-NH-CH ₂ -		-O-	-H
A-281.		-NH-(CH ₂) ₃ -	-CH ₂ -	-O-	-CH ₃
A-282.		-NH-(CH ₂) ₃ -	-CH ₂ -	-O-	-CH ₃
A-283.		-NH-(CH ₂) ₃ -	-CH ₂ -	-O-	-CH ₃
A-284.		-NH-(CH ₂) ₃ -	-CH ₂ -	-O-	-CH ₃
A-285.		-NH-(CH ₂) ₃ -	-CH ₂ -	-O-	-CH ₃
A-286.		-NH-(CH ₂) ₃ -	-CH ₂ -	-O-	-CH ₃
A-287.		-NH-(CH ₂) ₃ -	-CH ₂ -	-O-	-CH ₃

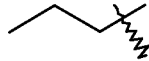
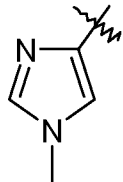
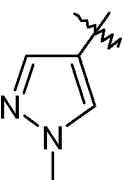
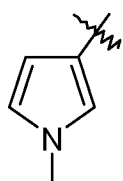
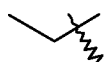
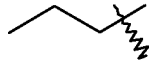
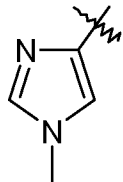
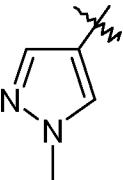
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-288.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-O-	-CH ₃
A-289.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-O-	-CH ₃
A-290.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-O-	-CH ₃
A-291.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-O-	-CH ₃
A-292.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-O-	-CH ₃
A-293.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-O-	-CH ₃
A-294.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-O-	-CH ₃
A-295.		-NH-(CH ₂) ₂ -	-CH ₂ -	-O-	-CH ₃
A-296.		-NH-(CH ₂) ₂ -	-CH ₂ -	-O-	-CH ₃
A-297.		-NH-(CH ₂) ₂ -	-CH ₂ -	-O-	-CH ₃
A-298.		-NH-(CH ₂) ₂ -	-CH ₂ -	-O-	-CH ₃

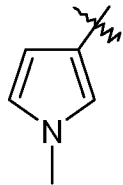
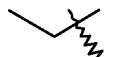
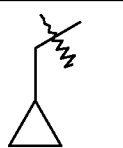
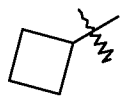
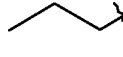
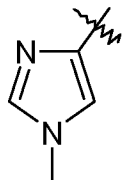
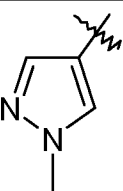
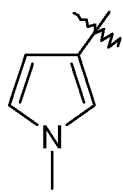
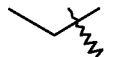
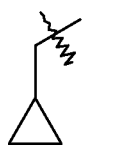
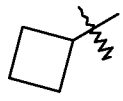
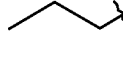
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-299.		-NH-(CH ₂) ₂ -	-CH ₂ -	-O-	-CH ₃
A-300.		-NH-(CH ₂) ₂ -	-CH ₂ -	-O-	-CH ₃
A-301.		-NH-(CH ₂) ₂ -	-CH ₂ -	-O-	-CH ₃
A-302.		-NH-CH ₂ -	-CH ₂ -	-O-	-CH ₃
A-303.		-NH-CH ₂ -	-CH ₂ -	-O-	-CH ₃
A-304.		-NH-CH ₂ -	-CH ₂ -	-O-	-CH ₃
A-305.		-NH-CH ₂ -	-CH ₂ -	-O-	-CH ₃
A-306.		-NH-CH ₂ -	-CH ₂ -	-O-	-CH ₃
A-307.		-NH-CH ₂ -	-CH ₂ -	-O-	-CH ₃
A-308.		-NH-CH ₂ -	-CH ₂ -	-O-	-CH ₃

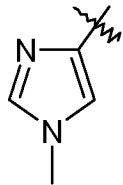
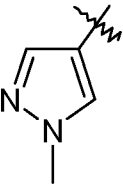
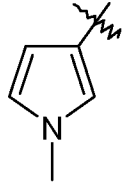
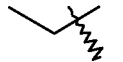
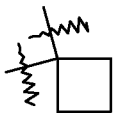
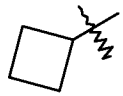
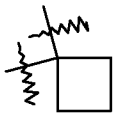
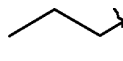
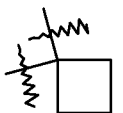
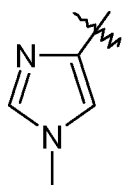
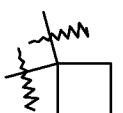
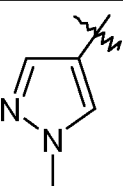
	R^1	$-Y-A^2-X^1-$	$>CR^{12a}R^{12b}$	A^3	R^4
A-309.		$-NH-(CH_2)_3-$		$-O-$	$-CH_3$
A-310.		$-NH-(CH_2)_3-$		$-O-$	$-CH_3$
A-311.		$-NH-(CH_2)_3-$		$-O-$	$-CH_3$
A-312.		$-NH-(CH_2)_3-$		$-O-$	$-CH_3$
A-313.		$-NH-(CH_2)_3-$		$-O-$	$-CH_3$
A-314.		$-NH-(CH_2)_3-$		$-O-$	$-CH_3$
A-315.		$-NH-(CH_2)_3-$		$-O-$	$-CH_3$
A-316.		$-NH-(CH_2)_2-O-$		$-O-$	$-CH_3$
A-317.		$-NH-(CH_2)_2-O-$		$-O-$	$-CH_3$
A-318.		$-NH-(CH_2)_2-O-$		$-O-$	$-CH_3$

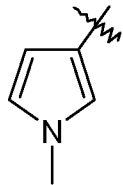
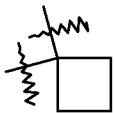
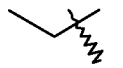
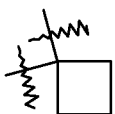
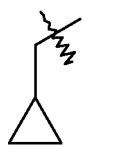
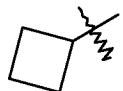
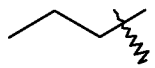
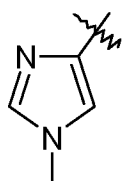
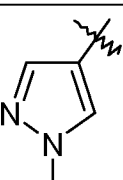
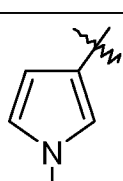
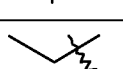
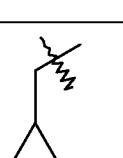
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-319.		-NH-(CH ₂) ₂ -O-		-O-	-CH ₃
A-320.		-NH-(CH ₂) ₂ -O-		-O-	-CH ₃
A-321.		-NH-(CH ₂) ₂ -O-		-O-	-CH ₃
A-322.		-NH-(CH ₂) ₂ -O-		-O-	-CH ₃
A-323.		-NH-(CH ₂) ₂ -		-O-	-CH ₃
A-324.		-NH-(CH ₂) ₂ -		-O-	-CH ₃
A-325.		-NH-(CH ₂) ₂ -		-O-	-CH ₃
A-326.		-NH-(CH ₂) ₂ -		-O-	-CH ₃
A-327.		-NH-(CH ₂) ₂ -		-O-	-CH ₃

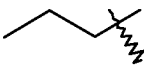
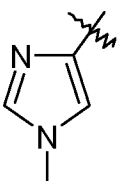
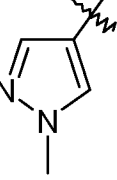
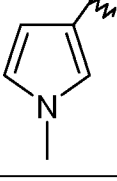
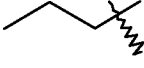
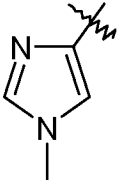
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-328.		-NH-(CH ₂) ₂ -		-O-	-CH ₃
A-329.		-NH-(CH ₂) ₂ -		-O-	-CH ₃
A-330.		-NH-CH ₂ -		-O-	-CH ₃
A-331.		-NH-CH ₂ -		-O-	-CH ₃
A-332.		-NH-CH ₂ -		-O-	-CH ₃
A-333.		-NH-CH ₂ -		-O-	-CH ₃
A-334.		-NH-CH ₂ -		-O-	-CH ₃
A-335.		-NH-CH ₂ -		-O-	-CH ₃
A-336.		-NH-CH ₂ -		-O-	-CH ₃
A-337.		-NH-(CH ₂) ₃ -	-CH ₂ -	-O-	-CH ₂ CH ₃

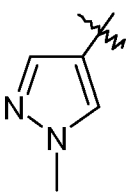
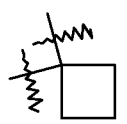
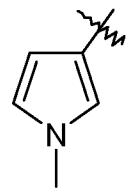
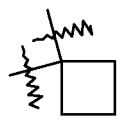
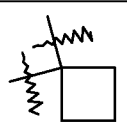
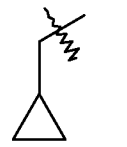
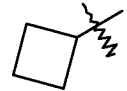
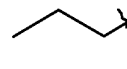
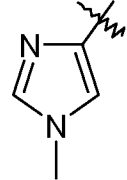
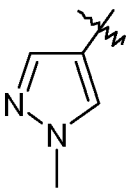
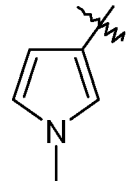
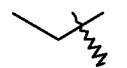
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-338.		-NH-(CH ₂) ₃ -	-CH ₂ -	-O-	-CH ₂ CH ₃
A-339.		-NH-(CH ₂) ₃ -	-CH ₂ -	-O-	-CH ₂ CH ₃
A-340.		-NH-(CH ₂) ₃ -	-CH ₂ -	-O-	-CH ₂ CH ₃
A-341.		-NH-(CH ₂) ₃ -	-CH ₂ -	-O-	-CH ₂ CH ₃
A-342.		-NH-(CH ₂) ₃ -	-CH ₂ -	-O-	-CH ₂ CH ₃
A-343.		-NH-(CH ₂) ₃ -	-CH ₂ -	-O-	-CH ₂ CH ₃
A-344.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-O-	-CH ₂ CH ₃
A-345.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-O-	-CH ₂ CH ₃
A-346.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-O-	-CH ₂ CH ₃
A-347.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-O-	-CH ₂ CH ₃
A-348.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-O-	-CH ₂ CH ₃

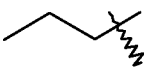
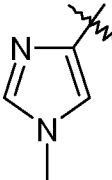
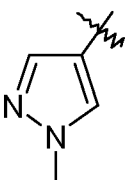
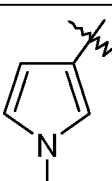
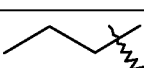
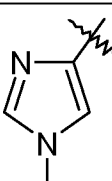
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-349.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-O-	-CH ₂ CH ₃
A-350.		-NH-(CH ₂) ₂ -O-	-CH ₂ -	-O-	-CH ₂ CH ₃
A-351.		-NH-(CH ₂) ₂ -	-CH ₂ -	-O-	-CH ₂ CH ₃
A-352.		-NH-(CH ₂) ₂ -	-CH ₂ -	-O-	-CH ₂ CH ₃
A-353.		-NH-(CH ₂) ₂ -	-CH ₂ -	-O-	-CH ₂ CH ₃
A-354.		-NH-(CH ₂) ₂ -	-CH ₂ -	-O-	-CH ₂ CH ₃
A-355.		-NH-(CH ₂) ₂ -	-CH ₂ -	-O-	-CH ₂ CH ₃
A-356.		-NH-(CH ₂) ₂ -	-CH ₂ -	-O-	-CH ₂ CH ₃
A-357.		-NH-(CH ₂) ₂ -	-CH ₂ -	-O-	-CH ₂ CH ₃
A-358.		-NH-CH ₂ -	-CH ₂ -	-O-	-CH ₂ CH ₃
A-359.		-NH-CH ₂ -	-CH ₂ -	-O-	-CH ₂ CH ₃
A-360.		-NH-CH ₂ -	-CH ₂ -	-O-	-CH ₂ CH ₃

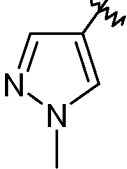
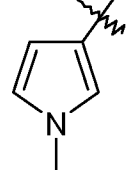
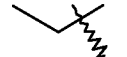
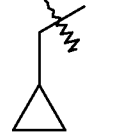
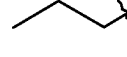
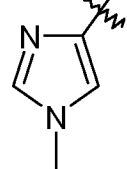
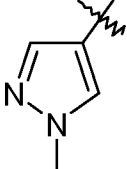
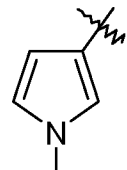
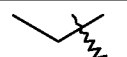
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-361.		-NH-CH ₂ -	-CH ₂ -	-O-	-CH ₂ CH ₃
A-362.		-NH-CH ₂ -	-CH ₂ -	-O-	-CH ₂ CH ₃
A-363.		-NH-CH ₂ -	-CH ₂ -	-O-	-CH ₂ CH ₃
A-364.		-NH-CH ₂ -	-CH ₂ -	-O-	-CH ₂ CH ₃
A-365.		-NH-(CH ₂) ₃ -		-O-	-CH ₂ CH ₃
A-366.		-NH-(CH ₂) ₃ -		-O-	-CH ₂ CH ₃
A-367.		-NH-(CH ₂) ₃ -		-O-	-CH ₂ CH ₃
A-368.		-NH-(CH ₂) ₃ -		-O-	-CH ₂ CH ₃
A-369.		-NH-(CH ₂) ₃ -		-O-	-CH ₂ CH ₃

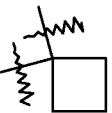
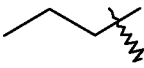
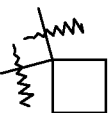
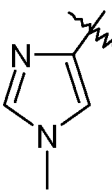
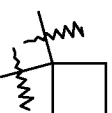
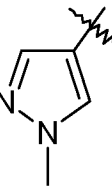
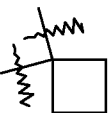
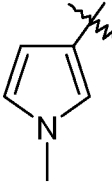
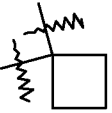
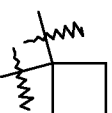
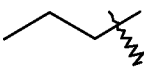
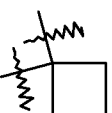
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-370.		-NH-(CH ₂) ₃ -		-O-	-CH ₂ CH ₃
A-371.		-NH-(CH ₂) ₃ -		-O-	-CH ₂ CH ₃
A-372.		-NH-(CH ₂) ₂ -O-		-O-	-CH ₂ CH ₃
A-373.		-NH-(CH ₂) ₂ -O-		-O-	-CH ₂ CH ₃
A-374.		-NH-(CH ₂) ₂ -O-		-O-	-CH ₂ CH ₃
A-375.		-NH-(CH ₂) ₂ -O-		-O-	-CH ₂ CH ₃
A-376.		-NH-(CH ₂) ₂ -O-		-O-	-CH ₂ CH ₃
A-377.		-NH-(CH ₂) ₂ -O-		-O-	-CH ₂ CH ₃
A-378.		-NH-(CH ₂) ₂ -O-		-O-	-CH ₂ CH ₃
A-379.		-NH-(CH ₂) ₂ -		-O-	-CH ₂ CH ₃

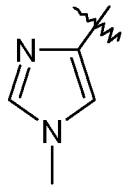
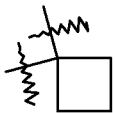
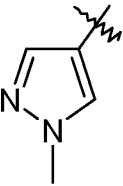
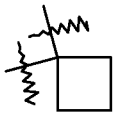
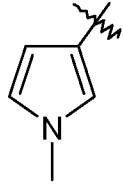
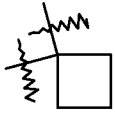
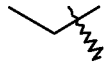
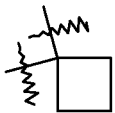
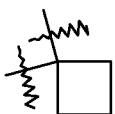
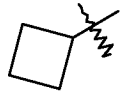
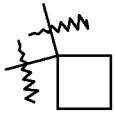
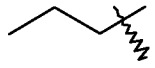
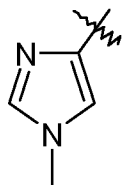
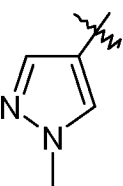
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-380.		-NH-(CH ₂) ₂ -		-O-	-CH ₂ CH ₃
A-381.		-NH-(CH ₂) ₂ -		-O-	-CH ₂ CH ₃
A-382.		-NH-(CH ₂) ₂ -		-O-	-CH ₂ CH ₃
A-383.		-NH-(CH ₂) ₂ -		-O-	-CH ₂ CH ₃
A-384.		-NH-(CH ₂) ₂ -		-O-	-CH ₂ CH ₃
A-385.		-NH-(CH ₂) ₂ -		-O-	-CH ₂ CH ₃
A-386.		-NH-CH ₂ -		-O-	-CH ₂ CH ₃
A-387.		-NH-CH ₂ -		-O-	-CH ₂ CH ₃
A-388.		-NH-CH ₂ -		-O-	-CH ₂ CH ₃
A-389.		-NH-CH ₂ -		-O-	-CH ₂ CH ₃

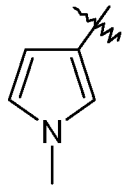
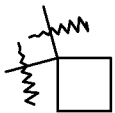
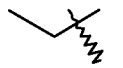
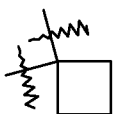
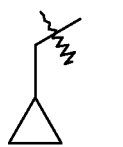
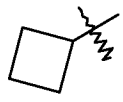
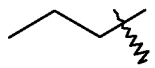
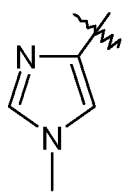
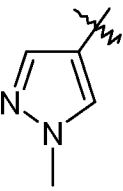
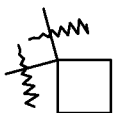
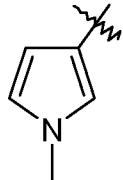
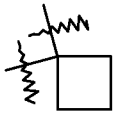
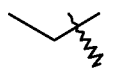
	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-390.		-NH-CH ₂ -		-O-	-CH ₂ CH ₃
A-391.		-NH-CH ₂ -		-O-	-CH ₂ CH ₃
A-392.		-NH-CH ₂ -		-O-	-CH ₂ CH ₃
A-393.		-NH-(CH ₂) ₃ -	-CH ₂ -	-O-	-CH ₂ CH ₂ CH ₃
A-394.		-NH-(CH ₂) ₃ -	-CH ₂ -	-O-	-CH ₂ CH ₂ CH ₃
A-395.		-NH-(CH ₂) ₃ -	-CH ₂ -	-O-	-CH ₂ CH ₂ CH ₃
A-396.		-NH-(CH ₂) ₃ -	-CH ₂ -	-O-	-CH ₂ CH ₂ CH ₃
A-397.		-NH-(CH ₂) ₃ -	-CH ₂ -	-O-	-CH ₂ CH ₂ CH ₃
A-398.		-NH-(CH ₂) ₃ -	-CH ₂ -	-O-	-CH ₂ CH ₂ CH ₃
A-399.		-NH-(CH ₂) ₃ -	-CH ₂ -	-O-	-CH ₂ CH ₂ CH ₃

	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-400.		-NH- (CH ₂) ₂ -O-	-CH ₂ -	-O-	-CH ₂ CH ₂ CH ₃
A-401.		-NH- (CH ₂) ₂ -O-	-CH ₂ -	-O-	-CH ₂ CH ₂ CH ₃
A-402.		-NH- (CH ₂) ₂ -O-	-CH ₂ -	-O-	-CH ₂ CH ₂ CH ₃
A-403.		-NH- (CH ₂) ₂ -O-	-CH ₂ -	-O-	-CH ₂ CH ₂ CH ₃
A-404.		-NH- (CH ₂) ₂ -O-	-CH ₂ -	-O-	-CH ₂ CH ₂ CH ₃
A-405.		-NH- (CH ₂) ₂ -O-	-CH ₂ -	-O-	-CH ₂ CH ₂ CH ₃
A-406.		-NH- (CH ₂) ₂ -O-	-CH ₂ -	-O-	-CH ₂ CH ₂ CH ₃
A-407.		-NH- (CH ₂) ₂ -	-CH ₂ -	-O-	-CH ₂ CH ₂ CH ₃
A-408.		-NH- (CH ₂) ₂ -	-CH ₂ -	-O-	-CH ₂ CH ₂ CH ₃
A-409.		-NH- (CH ₂) ₂ -	-CH ₂ -	-O-	-CH ₂ CH ₂ CH ₃
A-410.		-NH- (CH ₂) ₂ -	-CH ₂ -	-O-	-CH ₂ CH ₂ CH ₃

	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-411.		-NH-(CH ₂) ₂ -	-CH ₂ -	-O-	-CH ₂ CH ₂ CH ₃ - CH ₂ CH ₃
A-412.		-NH-(CH ₂) ₂ -	-CH ₂ -	-O-	-CH ₂ CH ₂ CH ₃
A-413.		-NH-(CH ₂) ₂ -	-CH ₂ -	-O-	-CH ₂ CH ₂ CH ₃
A-414.		-NH-CH ₂ -	-CH ₂ -	-O-	-CH ₂ CH ₂ CH ₃
A-415.		-NH-CH ₂ -	-CH ₂ -	-O-	-CH ₂ CH ₂ CH ₃
A-416.		-NH-CH ₂ -	-CH ₂ -	-O-	-CH ₂ CH ₂ CH ₃
A-417.		-NH-CH ₂ -	-CH ₂ -	-O-	-CH ₂ CH ₂ CH ₃
A-418.		-NH-CH ₂ -	-CH ₂ -	-O-	-CH ₂ CH ₂ CH ₃
A-419.		-NH-CH ₂ -	-CH ₂ -	-O-	-CH ₂ CH ₂ CH ₃
A-420.		-NH-CH ₂ -	-CH ₂ -	-O-	-CH ₂ CH ₂ CH ₃

	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-421.		-NH-(CH ₂) ₃ -		-O-	-CH ₂ CH ₂ CH ₃
A-422.		-NH-(CH ₂) ₃ -		-O-	-CH ₂ CH ₂ CH ₃
A-423.		-NH-(CH ₂) ₃ -		-O-	-CH ₂ CH ₂ CH ₃
A-424.		-NH-(CH ₂) ₃ -		-O-	-CH ₂ CH ₂ CH ₃
A-425.		-NH-(CH ₂) ₃ -		-O-	-CH ₂ CH ₂ CH ₃
A-426.		-NH-(CH ₂) ₃ -		-O-	-CH ₂ CH ₂ CH ₃
A-427.		-NH-(CH ₂) ₃ -		-O-	-CH ₂ CH ₂ CH ₃
A-428.		-NH-(CH ₂) ₂ -O-		-O-	-CH ₂ CH ₂ CH ₃
A-429.		-NH-(CH ₂) ₂ -O-		-O-	-CH ₂ CH ₂ CH ₃
A-430.		-NH-(CH ₂) ₂ -O-		-O-	-CH ₂ CH ₂ CH ₃

	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-431.		-NH-(CH ₂) ₂ -O-		-O-	-CH ₂ CH ₂ CH ₃
A-432.		-NH-(CH ₂) ₂ -O-		-O-	-CH ₂ CH ₂ CH ₃
A-433.		-NH-(CH ₂) ₂ -O-		-O-	-CH ₂ CH ₂ CH ₃
A-434.		-NH-(CH ₂) ₂ -O-		-O-	-CH ₂ CH ₂ CH ₃
A-435.		-NH-(CH ₂) ₂ -		-O-	-CH ₂ CH ₂ CH ₃
A-436.		-NH-(CH ₂) ₂ -		-O-	-CH ₂ CH ₂ CH ₃
A-437.		-NH-(CH ₂) ₂ -		-O-	-CH ₂ CH ₂ CH ₃
A-438.		-NH-(CH ₂) ₂ -		-O-	-CH ₂ CH ₂ CH ₃
A-439.		-NH-(CH ₂) ₂ -		-O-	-CH ₂ CH ₂ CH ₃

	R ¹	-Y-A ² -X ¹ -	>CR ^{12a} R ^{12b}	A ³	R ⁴
A-440.		-NH-(CH ₂) ₂ -		-O-	-CH ₂ CH ₂ CH ₃
A-441.		-NH-(CH ₂) ₂ -		-O-	-CH ₂ CH ₂ CH ₃
A-442.		-NH-CH ₂ -		-O-	-CH ₂ CH ₂ CH ₃
A-443.		-NH-CH ₂ -		-O-	-CH ₂ CH ₂ CH ₃
A-444.		-NH-CH ₂ -		-O-	-CH ₂ CH ₂ CH ₃
A-445.		-NH-CH ₂ -		-O-	-CH ₂ CH ₂ CH ₃
A-446.		-NH-CH ₂ -		-O-	-CH ₂ CH ₂ CH ₃
A-447.		-NH-CH ₂ -		-O-	-CH ₂ CH ₂ CH ₃
A-448.		-NH-CH ₂ -		-O-	-CH ₂ CH ₂ CH ₃

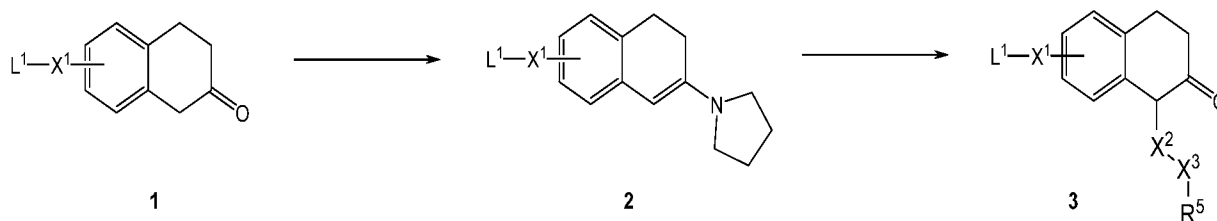
Further particular compounds of the present invention are the individual benzazepine derivatives of the formula (Id) as listed in tables 1 to 12 and physiologically tolerated salts thereof wherein the radical R¹-S(O)₂-Y-A²-X¹- is replaced by the radical -CN.

Further particular compounds of the present invention are the benzazepine derivatives 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 benzazepine precursors of the general formula 3, wherein X^1 is -O- or -S- and A^3 is optionally substituted alkylene (e.g. -CH₂-).

Scheme 1:



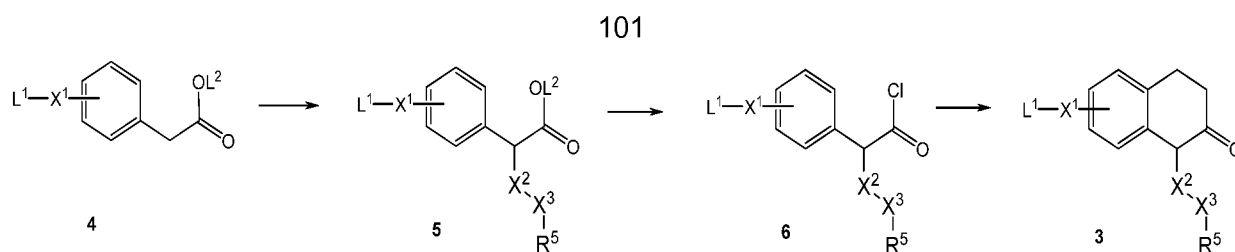
As shown in scheme 1, the compound of general formula 1 readily undergoes enamine alkylation to give the enamine 2 and after subsequent hydrolysis the compound of general formula 3.

In scheme 1, the variables X^2 , X^3 , R^5 are as defined herein, and L^1 represents an alkyl substituent (e.g. Me, Et, Bn).

The process depicted in scheme 1 is also useful for obtaining benzazepines, wherein X^1 is optionally substituted alkylene. In this case, L^1 is a group that represents, or can be converted into, the desired side chain $R^1-W-A^1-Q-Y-A^2$.

Alternatively, compounds of formula 3 can be prepared as described in scheme 2.

Scheme 2:

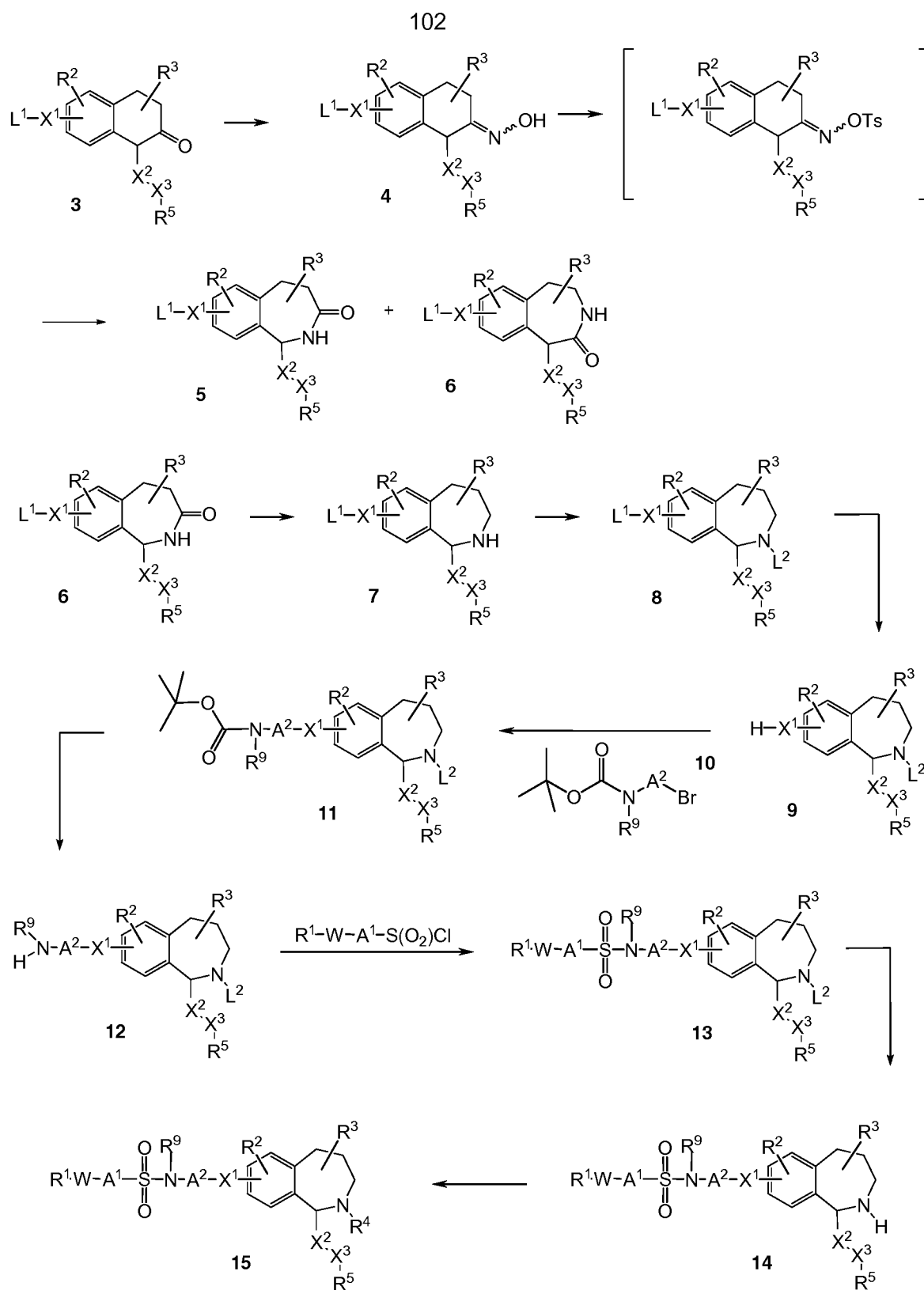


As shown in scheme 2, the compound of general formula 4 readily undergoes alkylation to give the compound of general formula 5. Conversion to the acid chloride and subsequent ring closure with ethylene in the presence of a Lewis acid (e.g. AlCl_3) affords compound 3 (e.g. J. Het. Chem., 23 (2), 343, 1986 and Bioorg. Med. Chem. Let, 17 (22), 6160, 2007).

In scheme 2, the variables X^1 , X^2 , X^3 , R^5 are as defined herein and L^1 and L^2 are suitable protecting groups (e.g. $\text{L}^1 = \text{Me, Et, Bn}$). Compounds 3 can be further converted to compounds of the general formula (I).

The process depicted in scheme 3 is useful for obtaining bezazepines, wherein X^1 is -O- or -S-, A^3 is optionally substituted alkylene (e.g. $-\text{CH}_2-$), Y is $-\text{NR}^9$ -, and Q is $-\text{S}(\text{O})_2$.

Scheme 3:



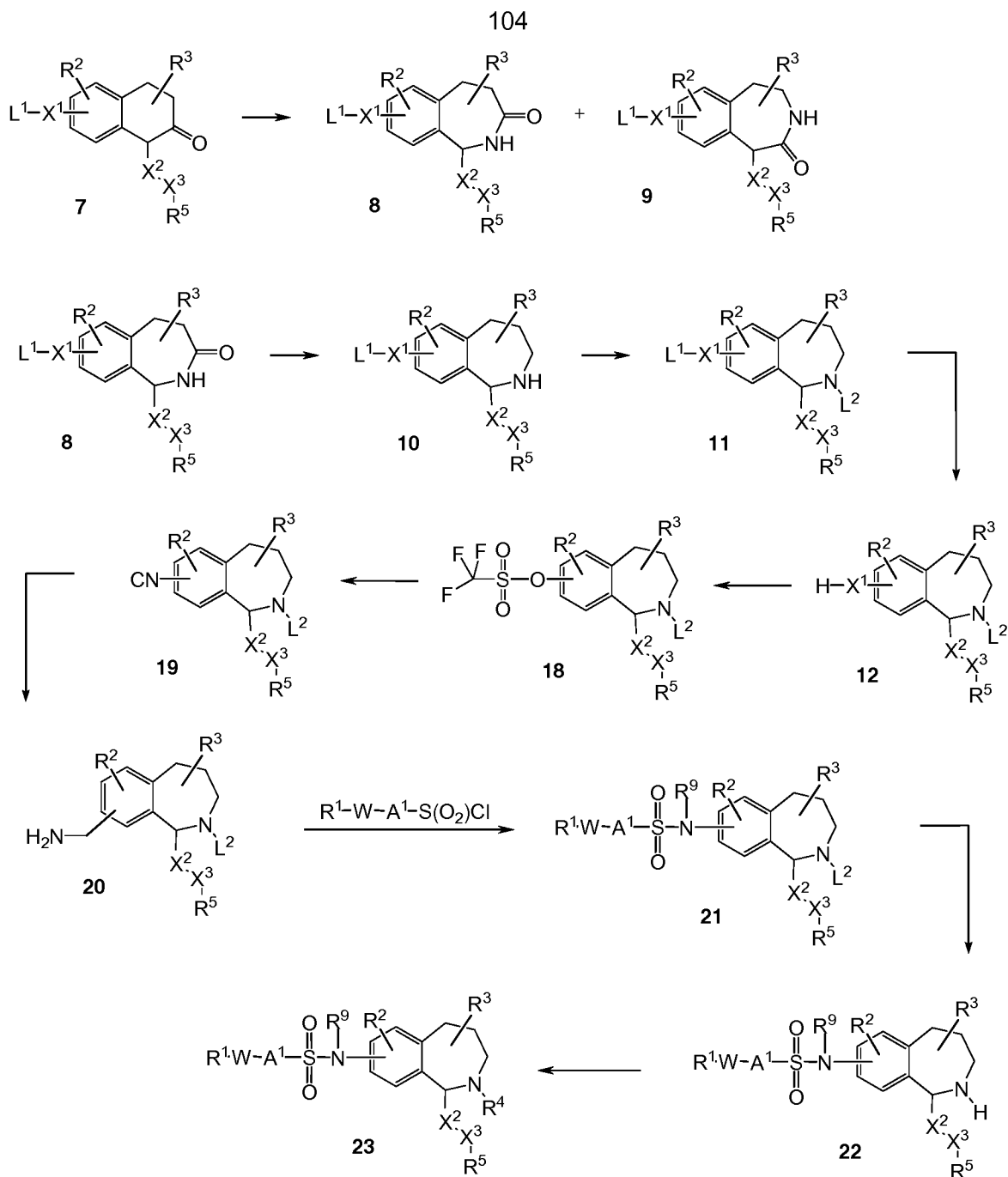
Compounds of the general formula 3 readily undergo condensation reactions to the corresponding mixtures of *E*- and *Z*-oxims 4. The oxims can be transferred into the tosylates, which subsequently undergo a Beckmann rearrangement to give a mixture of lactames of

the general formula 5 and 6 (e.g. Org. Lett. 2, 2373, 2000). Alternatively, the Beckmann rearrangement can be carried out under acidic conditions to convert the oxims 4 directly to the lactames 5 and 6. Lactames 5 and 6 can be separated (e.g. flash chromatography). Lactames 5 can be converted to the amines of the general formula 7 using LiAlH_4 or other well known reducing agents ($\text{BH}_3 \cdot \text{Me}_2\text{S}$). Protection of the amino group with a suitable protecting group (e.g. $\text{L}^2 = \text{COOEt}$) leads to compounds of the general formula 8.

In scheme 3, the variables R^1 , W, A^1 , R^2 , R^3 , R^4 , X^2 , X^3 , R^5 , R^9 , A^2 are as defined herein and L^1 and L^2 are suitable protecting groups (e.g. $\text{L}^1 = \text{Me}$, Et, Bn, or tBuMe_2Si ; $\text{L}^2 = \text{COOtBu}$ or COOEt).

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

Scheme 4:



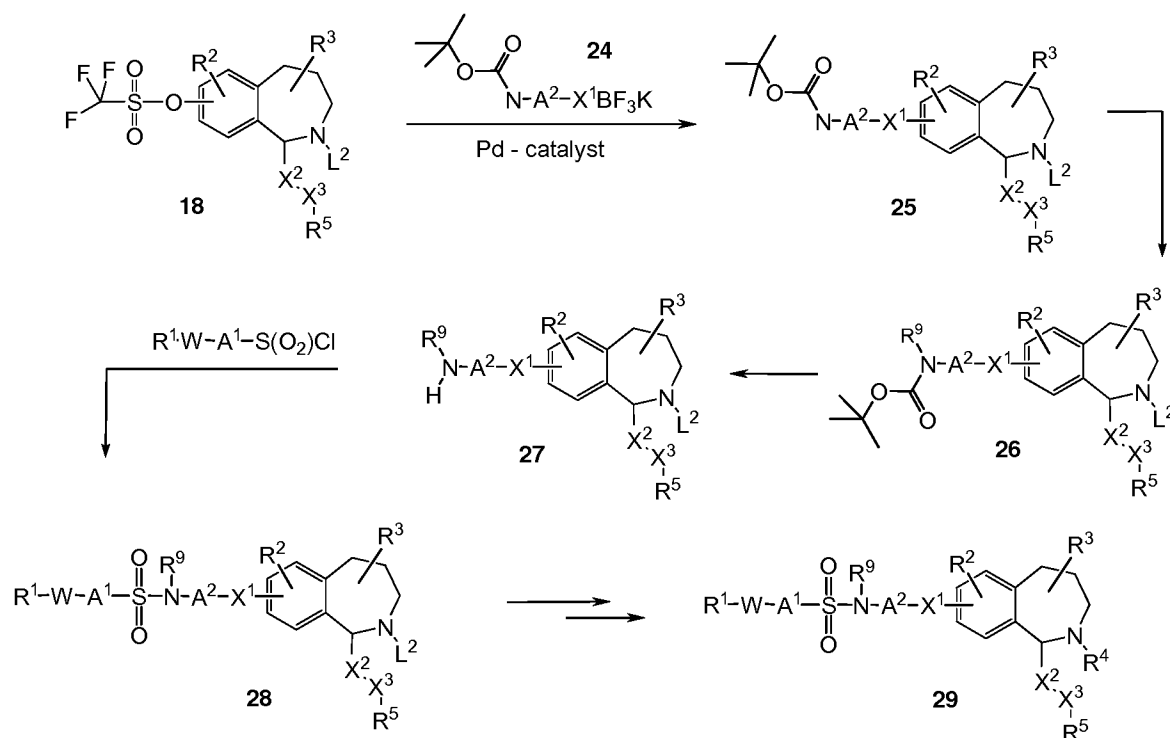
Instead of the triflate 18, the corresponding bromide, iodide, or nonaflate can be used to prepare compound 19.

5

In scheme 4, the variables R^1 , W , A^1 , R^2 , R^3 , R^4 , X^2 , X^3 , R^5 , R^9 are as defined herein, and L^1 and L^2 are a suitable protecting group (e.g. $L^1 = \text{Me}$, Et , Bn , or tBuMe_2Si ; $L^2 = \text{COO}^t\text{Bu}$ or COOEt).

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

5 Scheme 5:



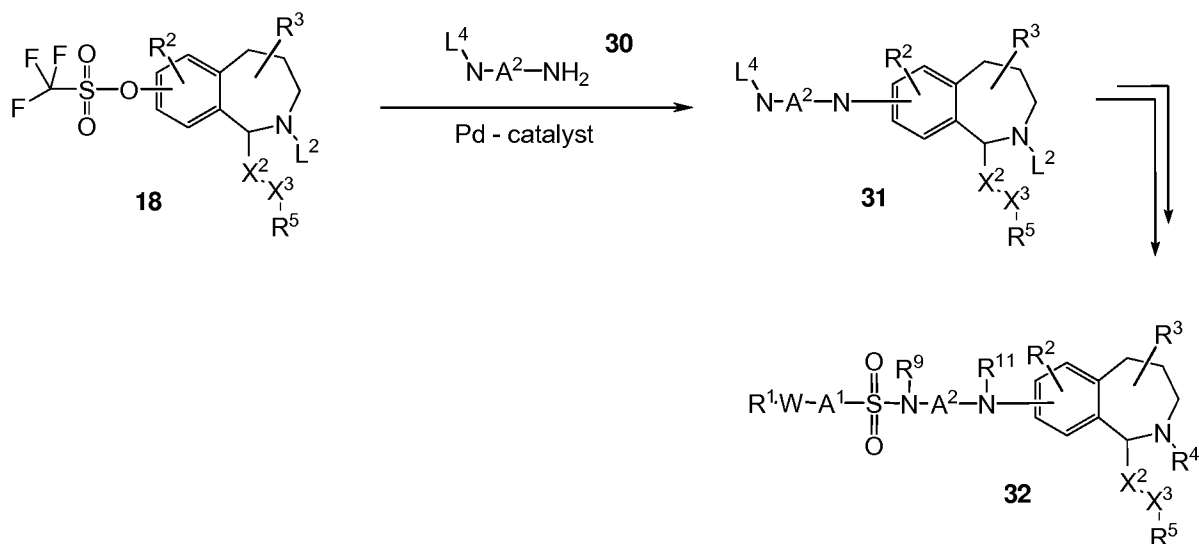
10 Instead of the trifluoroborate 24, the corresponding 9-borabicyclo[3.3.1]non-9-yl derivative can be used to prepare compound 25.

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

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

Scheme 6:

106

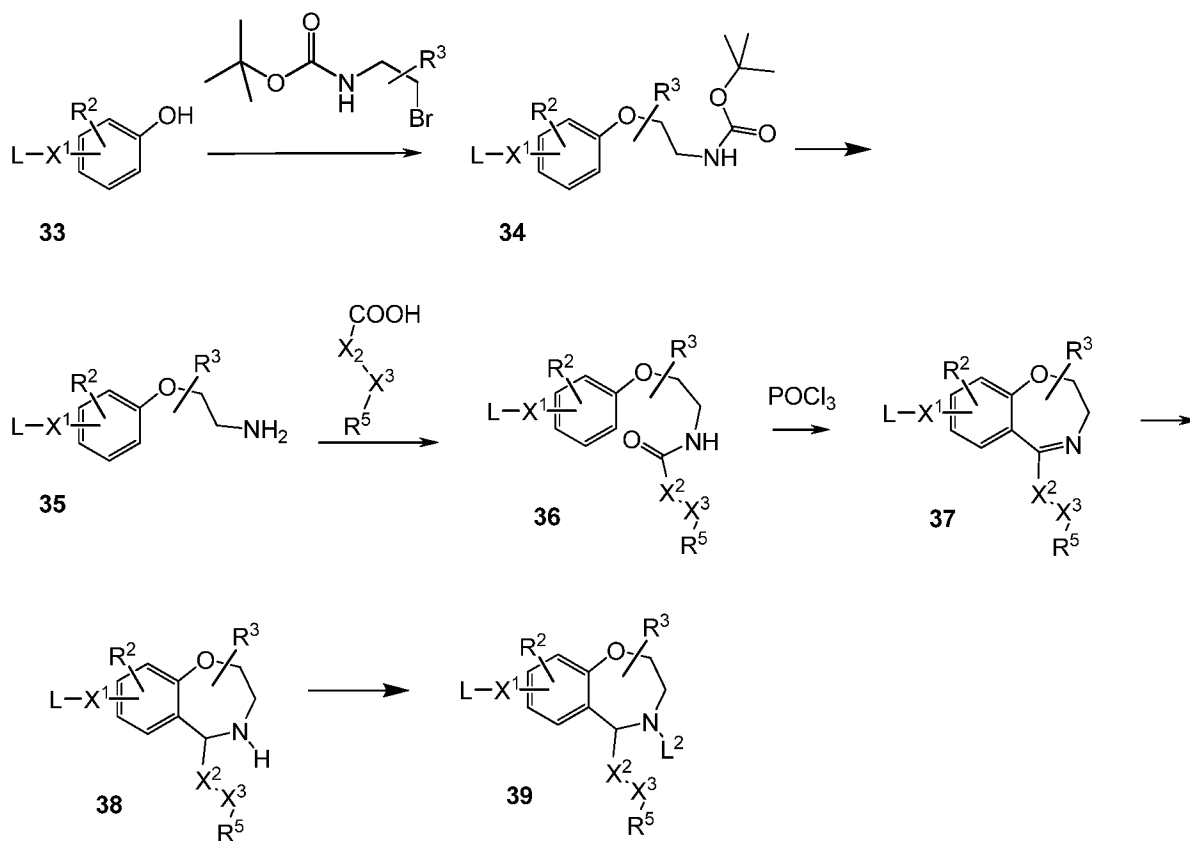


In scheme 6, the variables R^1 , W , A^1 , R^{11} , R^2 , R^3 , R^4 , X^2 , X^3 , R^5 , R^9 are as defined herein, and L^2 and L^4 are a suitable protecting group (e.g. L^2 , L^4 = COO^tBu or $COOEt$).

5

The process depicted in scheme 7 is useful for obtaining benzoxazepine precursors of the general formula 39, wherein X^1 is -O- or -S- and A^3 is -O-.

Scheme 7:



10

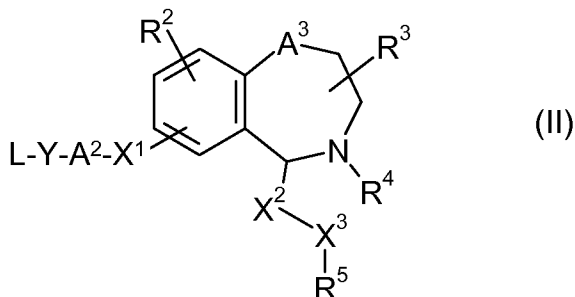
As shown in scheme 7, the compound of general formula 33 readily undergoes alkylation to give the compound of general formula 34. Deprotection leads to compounds of the general formula 35, which are converted via well known amide coupling reactions to the corresponding compounds of general formula 36 (e.g. EDC, DMAP). Amides of the general formula 36 undergo cyclization to imines of the formula 37 under Vilsmeier reaction conditions (e.g. POCl_3 , SOCl_2 , oxalyl chloride; see Chem. Ind. 1973, 870, Indian J. Chem., Sect. B (37B), 1998, 965, and Advances in Organic Chemistry (9), Pt. 1, 1976, 225). Reduction of imins of the general formula 37 (e.g. with NaBH_4) readily gives the corresponding amines of general formula 38. Protection of the free amine with a suitable protecting group (e.g. $\text{L}^2 = \text{COO}^t\text{Bu}$) yields compounds of the general formula 39. Introduction of the various side chains is performed as already described for the benzazepine derivatives in schemes 4 to 6.

In scheme 7, the variables R^2 , R^3 , R^4 , X^2 , X^3 , R^5 are as defined herein, L represents an alkyl substituent (e.g. Me, Et, Bn) and L^2 is a suitable protecting group (e.g. $\text{L}^2 = \text{COO}^t\text{Bu}$ or COOEt).

The process depicted in scheme 7 is also useful for obtaining benzazepines derivatives of formula (I), wherein A^3 is -S-, or NR^{16} .

The acid addition salts of the benzazepine derivatives 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 benzazepines derivatives of formula (II):



wherein L is an amino-protecting group, Y is NR^9 , and A^2 , X^1 , R^2 , A^3 , R^3 , R^4 , X^2 , X^3 , R^5 are defined as herein 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 arylalkylcarbonyl (e.g., benzylcarbonyl), optionally substituted alkoxycarbonyl (e.g., methoxycarbonyl or tert-butyloxycarbonyl), optionally substituted aryloxycarbonyl (e.g. phenoxycarbonyl) or optionally substituted arylalkoxycarbonyl.

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 $IC_{50} < 1 \mu\text{Mol}$, more preferably at a level of $IC_{50} < 0.5 \mu\text{Mol}$, particularly preferably at a level of $IC_{50} < 0.2 \mu\text{Mol}$ and most preferably at a level of $IC_{50} < 0.1 \mu\text{Mol}$.

The compounds of formula (I) display good to moderate metabolic stability.

The metabolic stability of a compound can be measured for example by incubating a solution of this compound with liver microsomes from particular species (for example rat, dog or human) and determining the half-life of the compound under these conditions (RS Obach, Curr Opin Drug Discov Devel. 2001 , 4, 36-44). It is possible in this connection to conclude from an observed longer half-life that the metabolic stability of the compound is improved. The stability in the presence of human liver microsomes is of particular interest because it makes it possible to predict the metabolic degradation of the compound in the human liver. Compounds with increased metabolic stability (measured in the liver microsome test) are therefore probably also degraded more slowly in the liver. The slower metabolic degradation in the liver may lead to higher and/or longer-lasting concentrations (active levels) of the compound in the body, so that the elimination half-life of the com-

pounds of the invention is increased. Increased and/or longer-lasting active levels may lead to a better activity of the compound in therapeutic treatment. In addition, an improved metabolic stability may lead to an increased bioavailability after oral administration, because the compound is subject, after absorption in the intestine, to less metabolic degradation in the liver (so-called first pass effect). An increased oral bioavailability may, owing to an increased concentration (active level) of the compound, lead to a better activity of the compound after oral administration.

Amongst the compounds of the formula (I) those are particularly preferred which display good to moderate metabolic stability towards human liver microsomes.. In particular, compounds of the formula (I) are preferred which display a microsomal clearance at a level of $mCl < 1000 \mu\text{l/min/mg}$, more preferably at a level of $mCl < 500 \mu\text{l/min/mg}$, particularly preferably at a level of $mCl < 100 \mu\text{l/min/mg}$ and most preferably at a level of $mCl < 50 \mu\text{l/min/mg}$.

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

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

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

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

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

- 5 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
10 (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,
15 HIV disease, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jacob disease, perinatal hypoxia, other general medical conditions or substance abuse); delirium, amnesic 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
20 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 amnesic 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
25 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
35 postural tremor), Gilles de la Tourette's syndrome, epilepsy, muscular spasms and disorder

ders 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
5 generalised myoclonus and focal myoclonus), tics (including simple tics, complex tics and symptomatic tics), and dystonia (including generalised dystonia such as idiopathic 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
10 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
15 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.

20 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.

25 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
30 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
35 therefore tend to respond to different types of treatments. Acute pain can be somatic or visceral in nature. Somatic pain tends to be a well localised, constant pain and is described as sharp, aching, throbbing or gnawing. Visceral pain, on the other hand, tends to be vague in distribution, paroxysmal in nature and is usually described as deep, aching, squeezing or colicky in nature. Examples of acute pain include post-operative pain, pain

associated with trauma and the pain of arthritis. Acute pain usually responds to treatment with opioids or non-steroidal anti-inflammatory drugs.

Chronic pain, in contrast to acute pain, is described as burning, electric, tingling and shooting in nature. It can be continuous or paroxysmal in presentation. The hallmarks of chronic pain are chronic allodynia and hyperalgesia. Allodynia is pain resulting from a stimulus that normally does not elicit a painful response, such as a light touch. Hyperalgesia is an increased sensitivity to normally painful stimuli. Primary hyperalgesia occurs immediately within the area of the injury. Secondary hyperalgesia occurs in the undamaged area surrounding the injury. Examples of chronic pain include complex regional pain syndrome, pain arising from peripheral neuropathies, post-operative pain, chronic fatigue syndrome pain, tension-type headache, pain arising from mechanical nerve injury and severe pain associated with diseases such as cancer, metabolic disease, 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 sub-optimal pain control rather than suffer these distressing side-effects. Furthermore, these side-effects often result in patients requiring extended hospitalisation. Opioids are highly addictive and are scheduled drugs in many territories.

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

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

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

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

5 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.

10 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.

15 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.

20 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.

25 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.

35 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

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devices can also be used for administering inhibitors according to the invention. In addition, it is also possible to use liposomes or microspheres.

5 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.

10 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
15 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.
20

25 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;
- 30 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;
- 35 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,
- 40 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;

- 5 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
10 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
15 current invention. In one embodiment of adjunctive therapeutic administration as described herein, a patient is typically stabilized on a therapeutic administration of one or more of the components for a period of time and then receives administration of another component.

20 The combination therapies of the invention may also be administered simultaneously. By simultaneous administration is meant a treatment regime wherein the individual components are administered together, either in the form of a single pharmaceutical composition or device comprising or containing both components, or as separate compositions or devices, each comprising one of the components, administered simultaneously. Such combinations of the separate individual components for simultaneous combination may be
25 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
30 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
35 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
40 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 thiothix-

ene 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.

5

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 trade-
10 name 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 Phar-
15 maceutical Partners, Pasadena); thiothixene (available under the tradename NAVANE®, from Pfizer); trifluoperazine (10-[3-(4-methyl-1-piperaziny)propyl]-2- (trifluoro-methyl)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, Rox-
20 ane, HiTech, Teva, and Alharma) ; 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 trade-
25 name SPARINE®), triflurpromazine (available under the tradename VESPRI N®), chlorprothixene (available under the tradename TARACTAN®), droperidol (available under the tradename INAPSINE®), acetophenazine (available under the tradename TINDAL®), prochlorperazine (available under the tradename COMPAZINE®), methotrimeprazine (avail-
able under the tradename NOZINAN®), pipotiazine (available under the tradename PI-
POTRIL®), ziprasidone, and hoperidone.

30

In a further aspect, the invention provides a method of treatment of a neurodegenerative disorder such as Alzheimer Disease by adjunctive therapeutic administration of com-
pounds 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
35 a further aspect, the invention provides the use of compounds of formula (I) in the manu-
facture 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 dis-
order such as Alzheimer Disease. The invention further provides compounds of formula (I)
40 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.

- 5 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).

- 20 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.

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Examples of agents suitable for the treatment of a neurodegenerative disorder such as Alzheimer Disease that are useful in the present invention include, but are not limited to: cholinesterase inhibitors, agents targeting nicotinic or muscarinic acetylcholine receptors, NMDA receptors, amyloid formation, mitochondrial dysfunctions, disease associated cal-

10 pain activity, neuroinflammation, 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.

15 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.

20

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.

25 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

30 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.

35 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).

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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).

- 5 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), anti-convulsant 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, remifentanyl, 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.

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

- 10 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.

- 15 Suitable tricyclic antidepressants which may be used in combination with a compound of the invention include imipramine, amitriptyline, chlomipramine and nortriptyline.

- 20 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.

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

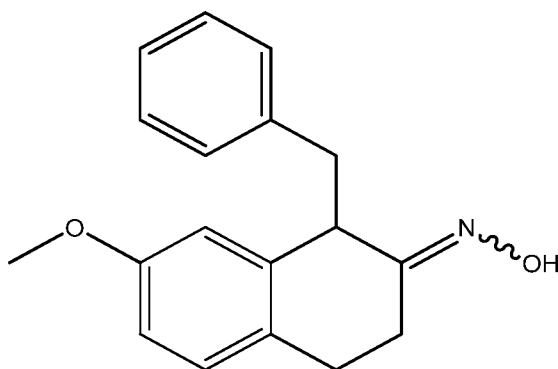
The compounds were characterized by mass spectrometry, generally recorded via HPLC-MS in a fast gradient on C18-material (electrospray-ionisation (ESI) mode).

30 Preparation Examples

Example 1 (for reference purposes): 1-Benzyl-8-methoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepine

1.1 1-benzyl-7-methoxy-3,4-dihydronaphthalen-2(1H)-one oxime

122

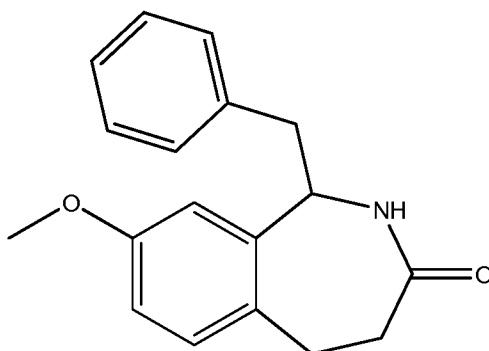


To a solution of 4.47 mmol of 1-benzyl-7-methoxy-3,4-dihydronaphthalen-2(1H)-one in 15 ml ethanol were added 5.59 mmol hydroxylamine hydrochloride (dissolved in 3 ml water). The solution was stirred at 65°C for 1.5 h. The mixture was cooled to RT and concentrated. The residue was dissolved in methyl tert-butylether and washed with water (2x), dried over MgSO₄ and filtered. Evaporation of the solvent gave 1.29 g of 1-benzyl-7-methoxy-3,4-dihydronaphthalen-2(1H)-one oxime (mixture of *E*- and *Z*-isomer, 100 %).

ESI-MS [M+H⁺] = 282Calculated for C₁₈H₁₉NO₂ = 281

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1.2 1-Benzyl-8-methoxy-4,5-dihydro-1H-benzo[c]azepin-3(2H)-one



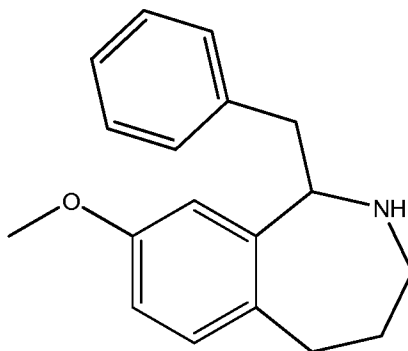
To a solution of 8.46 mmol of p-toluenesulfonylchloride, 8.4 mmol triethylamine and 0.16 mmol of dimethylaminopyridine in 5 ml of dichloromethane was added a solution of 945 mg of 1-benzyl-7-methoxy-3,4-dihydronaphthalen-2(1H)-one oxime in 5 ml dichloromethane. The solution was stirred at room temperature over night. The mixture was diluted with dichloromethane and washed with water and saturated NaHCO₃ solution. The combined organic layers were dried over MgSO₄ and filtered. Evaporation of the solvent gave 1.9 g of crude material that was purified by flash chromatography to yield 637 mg of the desired isomer 1-benzyl-8-methoxy-4,5-dihydro-1H-benzo[c]azepin-3(2H)-one (67%) and 248 mg of its regioisomer 1-benzyl-8-methoxy-4,5-dihydro-1H-benzo[d]azepin-2(3H)-one (26 %).

15

20

ESI-MS [M+H⁺] = 282Calculated for C₁₈H₁₉NO₂ = 281

1.3 1-Benzyl-8-methoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepine

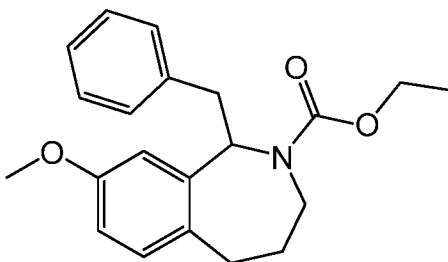


To a solution of 2.17 mmol of 1-benzyl-8-methoxy-4,5-dihydro-1H-benzo[c]azepin-3(2H)-one in tetrahydrofuran under nitrogen atmosphere was added 3.25 mmol of lithiumaluminumhydride as 1 M solution in tetrahydrofuran. The solution was heated to reflux and stirred for 1.5 h. The mixture was cooled to room temperature and water (1 ml) was carefully added. The mixture was concentrated and the residue was dissolved in ethyl acetate. The organic phase was extracted with acidified water (acidified with 1 M HCl, 4x). To the combined aqueous phase was added NaOH (50%) until basic and ethyl acetate. The suspension was filtered over celite. The residue was washed with water and ethyl acetate. Phases were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over MgSO_4 and filtered. Evaporation of the solvent gave 439 mg of crude material that was purified by flash chromatography to yield 399 mg of 1-benzyl-8-methoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepine (69%).

ESI-MS $[\text{M}+\text{H}^+] = 268$ Calculated for $\text{C}_{18}\text{H}_{21}\text{NO} = 267$

Example 2: N-(2-(1-Benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)ethyl)-1-methyl-1H-imidazole-4-sulfonamide

2.1 Ethyl 1-benzyl-8-methoxy-4,5-dihydro-1H-benzo[c]azepine-2(3H)-carboxylate



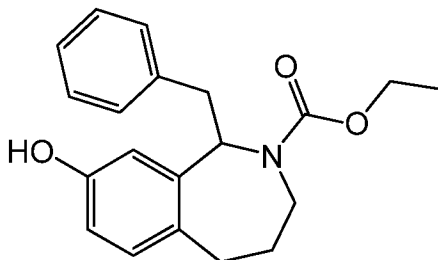
To a solution of 0.97 mmol of 1-benzyl-8-methoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepine in 10 ml dichloromethane under nitrogen atmosphere were added 1.17 mmol dimethyl amino pyridine and 1.12 mmol ethyl carbonochloridate and the mixture was stirred at room temperature for 1 h. The mixture was diluted with methylenechloride and washed

with saturated NH_4Cl solution and brine. The combined organic layers were dried over MgSO_4 and filtered. Evaporation of the solvent gave 248 mg of 1-benzyl-8-methoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepine (75 %).

5 ESI-MS $[\text{M}+\text{H}^+] = 340$

Calculated for $\text{C}_{21}\text{H}_{25}\text{NO}_3 = 339$

2.2 Ethyl 1-benzyl-8-hydroxy-4,5-dihydro-1H-benzo[c]azepine-2(3H)-carboxylate

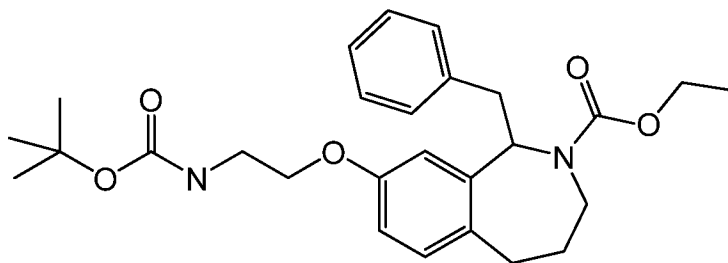


To a solution of 0.73 mmol 1-benzyl-8-methoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepine in
10 7 ml dichloromethylene under nitrogen atmosphere were added 2.20 mmol borontribro-
mide (1M solution in dichloromethane) at 0°C and stirred for 2 h. To the mixture was
added saturated solution of NaHCO_3 . Phases were separated and the aqueous phase
was extracted with ethyl acetate. The combined organic layers were washed with water,
15 dried over MgSO_4 and filtered. Evaporation of the solvent gave 242 mg of 11-benzyl-8-
hydroxy-4,5-dihydro-1H-benzo[c]azepine-2(3H)-carboxylate (100 %).

ESI-MS $[\text{M}+\text{H}^+] = 326$

Calculated for $\text{C}_{20}\text{H}_{23}\text{NO}_3 = 325$

2.3 ethyl 2-(1-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)ethylcarbamate



20

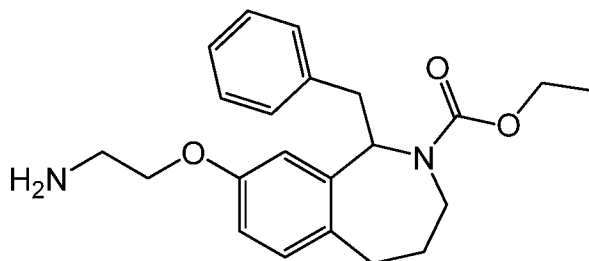
To a suspension of 1.88 mmol sodium hydride (60% in mineral oil) in 2 ml dimethyl
acetamide under nitrogen atmosphere was added a solution of 0.74 mmol 11-benzyl-8-
hydroxy-4,5-dihydro-1H-benzo[c]azepine-2(3H)-carboxylate in 5 ml dimethyl acetamide at
room temperature and stirred for 1 h. Then, a solution of 2.23 mmol tert-butyl 2-
25 bromoethylcarbamate in 1 ml dimethyl acetamide was added and the mixture was stirred
at room temperature for 2 d. 1.88 mmol of sodium hydride were added followed by 2.23
mmol of tert-butyl 2-bromoethylcarbamate in 1 ml dimethyl acetamide. The mixture was
stirred at room temperature for additional 4 d. 1.88 mmol of sodium hydride were added
followed by 2.23 mmol of tert-butyl 2-bromoethylcarbamate in 1 ml dimethyl acetamide.
30 The mixture was stirred at room temperature for additional 2 d. The mixture was poured

onto water and extracted with diethyl ether (3x). The combined organic layers were washed with water, dried over MgSO_4 and filtered. Evaporation of the solvent gave 1.17 g mg of crude material that was purified by flash chromatography to yield 359 mg of ethyl 2-(1-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)ethylcarbamate (100 %).

5

ESI-MS [M^+ -Boc] = 369Calculated for $\text{C}_{27}\text{H}_{36}\text{N}_2\text{O}_5$ = 468

2.4 Ethyl 8-(2-aminoethoxy)-1-benzyl-4,5-dihydro-1H-benzo[c]azepine-2(3H)-carboxylate



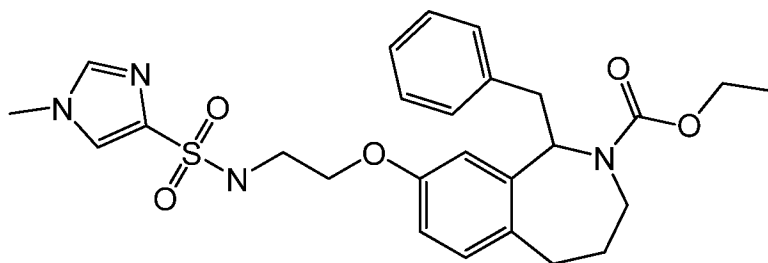
10

To a solution of 0.46 mmol of ethyl 2-(1-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)ethylcarbamate in 3 ml dichloromethane were added 4.57 mmol of a 5-6 N solution of HCl in isopropanol. The mixture was stirred at room temperature over night. The mixture was heated to 40°C and stirred for additional 2 h. The solvent was evaporated to give 151 mg of crude 2-(1-benzyl-2-(ethoxycarbonyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)ethanaminium chloride (82 %).

15

ESI-MS [M^+ +H] = 369Calculated for $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_3$ = 368

20 2.5 Ethyl 1-benzyl-8-(2-(1-methyl-1H-imidazole-4-sulfonamido)ethoxy)-4,5-dihydro-1H-benzo[c]azepine-2(3H)-carboxylate



25

To a solution of 0.12 mmol 2-(1-benzyl-2-(ethoxycarbonyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)ethanaminium chloride in 3 ml dichloromethane were added 0.33 mmol dimethylaminopyridine and 0.17 mmol 1-methyl-1H-imidazole-4-sulfonyl chloride. The mixture was stirred at room temperature over night. The mixture was diluted with ethyl acetate and washed with NH_4Cl solution (2x), water (1x), and brine (1x). The organic layer was dried over MgSO_4 and filtered. Evaporation of the solvent gave 66 mg of crude material that was purified by flash chromatography to yield 60 mg of ethyl 1-benzyl-8-(2-

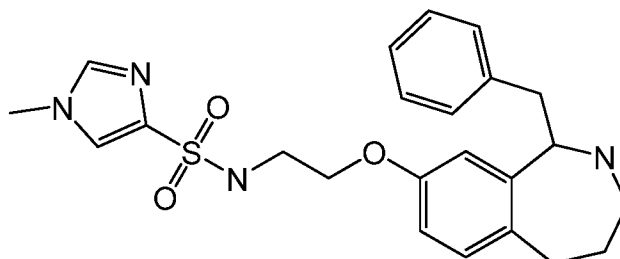
(1-methyl-1H-imidazole-4-sulfonamido)ethoxy)-4,5-dihydro-1H-benzo[c]azepine-2(3H)-carboxylate (95 %).

ESI-MS $[M+H]^+$ = 513

Calculated for $C_{26}H_{32}N_4O_5S$ = 512

5

2.6 N-(2-(1-Benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)ethyl)-1-methyl-1H-imidazole-4-sulfonamide



0.11 mmol of ethyl 1-benzyl-8-(2-(1-methyl-1H-imidazole-4-sulfonamido)ethoxy)-4,5-dihydro-1H-benzo[c]azepine-2(3H)-carboxylate were dissolved in a solution of potassium hydroxide in ethanol (20 %). The solution was heated in the microwave at 100°C for 3 h. The mixture was diluted with brine and extracted with ethyl acetate (3x). The combined organic layers were concentrated in vacuo to give 96 mg of crude material that was purified by flash chromatography to yield 37 mg of N-(2-(1-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)ethyl)-1-methyl-1H-imidazole-4-sulfonamide (77 %).

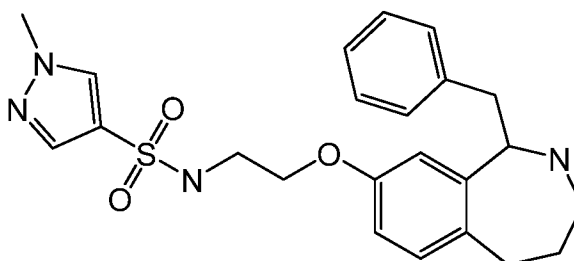
15

ESI-MS $[M+H]^+$ = 441

Calculated for $C_{23}H_{28}N_4O_3S$ = 440

Example 3: N-(2-(1-Benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)ethyl)-1-methyl-1H-pyrazole-4-sulfonamide

20



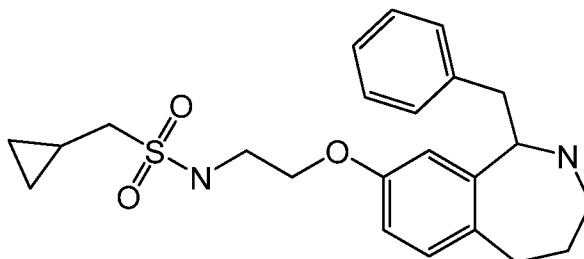
N-(2-(1-Benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)ethyl)-1-methyl-1H-pyrazole-4-sulfonamide was prepared in analogy to example 2 using 1-methyl-1H-pyrazole-4-sulfonyl chloride in place of 1-methyl-1H-imidazole-4-sulfonyl chloride.

25

ESI-MS $[M+H]^+$ = 441

Calculated for $C_{23}H_{28}N_4O_3S$ = 440

Example 4: N-(2-(1-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)ethyl)-1-cyclopropylmethanesulfonamide

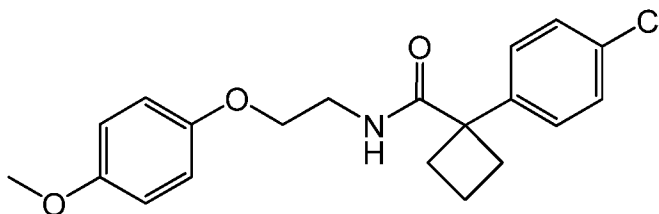


- 5 N-(2-(1-Benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)ethyl)-1-cyclopropylmethanesulfonamide was prepared in analogy to example 2 using cyclopropylmethanesulfonyl chloride in place of 1-methyl-1H-imidazole-4-sulfonyl chloride.

ESI-MS $[M+H]^+$ = 415 Calculated for $C_{23}H_{30}N_2O_3S$ = 414

- 10 Example 5 (for reference purposes only): 5-(1-(4-Chlorophenyl)cyclobutyl)-7-methoxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine hydrochloride

5.1 1-(4-Chlorophenyl)-N-(2-(4-methoxyphenoxy)ethyl)cyclobutanecarboxamide

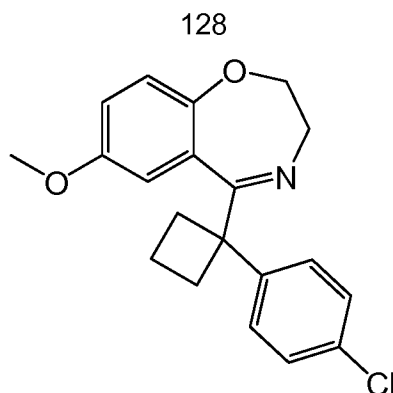


- 15 To a solution of 5.74 mmol of 2-(3-methoxy-phenyl)-ethylamine and 10.97 mmol of 4-dimethylaminopyridine in 400 ml dichloromethane were added 5.22 mmol 1-(4-chlorophenyl)-cyclobutanecarboxylic acid and the mixture was cooled to 4°C. EDC was added and the mixture was allowed to warm to room temperature within 45 min. The mixture was stirred at room temperature for additional 60 h. The organic phase was washed with water
20 (3x) and brine, dried over Na_2SO_4 , and filtered. Evaporation of the solvent gave the crude material, which was purified by flash chromatography to yield 1.87 g of 1-(4-chlorophenyl)-N-(2-(4-methoxyphenoxy)ethyl)cyclobutanecarboxamide (99 %).

ESI-MS $[M+H]^+$ = 360 Calculated for $C_{20}H_{22}ClNO_3$ = 359

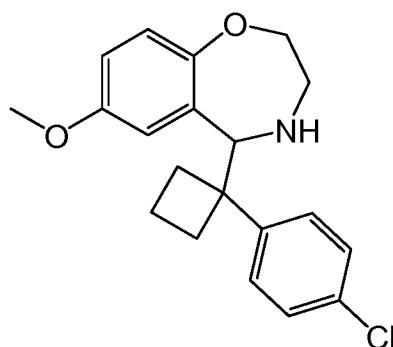
25

5.2 5-(1-(4-Chlorophenyl)cyclobutyl)-7-methoxy-2,3-dihydrobenzo[f][1,4]oxazepine



To a solution of 2.92 mmol of 1-(4-chlorophenyl)-N-(2-(4-methoxyphenoxy)ethyl)cyclobutanecarboxamide in 2 ml acetonitrile were added 114.78 mmol POCl₃ and the mixture was stirred in the microwave at 135°C for 2 h. The mixture was concentrated and the residue was dissolved in ethyl acetate. The organic phase was washed with water (3x) and brine, dried over Na₂SO₄, and filtered and concentrated to give 0.8 g of a light yellow solid. The crude material was purified by flash chromatography to yield 0.15 g of 5-(1-(4-chlorophenyl)cyclobutyl)-7-methoxy-2,3-dihydrobenzo[f][1,4]oxazepine (15 %).

5.3 5-(1-(4-Chlorophenyl)cyclobutyl)-7-methoxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine hydrochloride

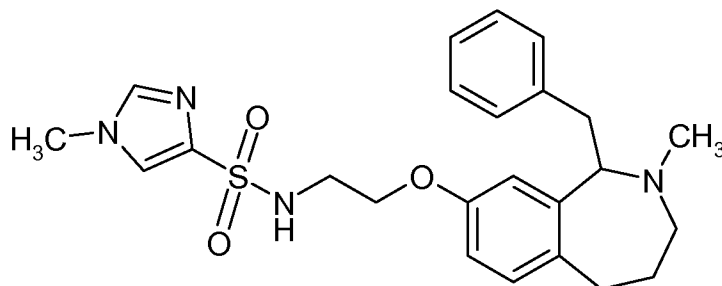


To a solution of 0.51 mmol of 5-(1-(4-chlorophenyl)cyclobutyl)-7-methoxy-2,3-dihydrobenzo[f][1,4]oxazepine in 5 ml methanol and 0.1 ml water were added 1.00 mmol sodium borohydride and the mixture was stirred at room temperature over night. The mixture was concentrated and the residue was dissolved in methylene chloride and water was added. The phases were separated using a Chromabond® PTS column. The aqueous phase was extracted with methylene chloride (1x). The combined organic phases were dried over Na₂SO₄, and filtered and concentrated to give 0.18 g of a crude material, which was purified by flash chromatography. To the combined fractions was added a solution of hydrogen chloride in 2-propanol and concentrated. The residue was dissolved in methanol and concentrated (2x). The material was further purified by flash chromatography to yield 14 mg of 5-(1-(4-chlorophenyl)cyclobutyl)-7-methoxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine hydrochloride as a white solid (HCl-salt, 15 %).

ESI-MS [M+H⁺] = 344

Calculated for C₂₀H₂₂Cl₁NO₂ = 343

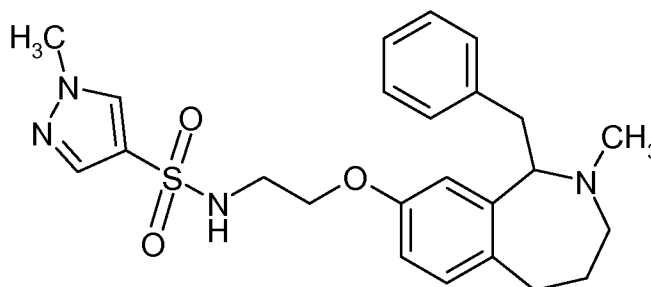
Example 6: 1-Methyl-1H-imidazole-4-sulfonic acid [2-(1-benzyl-2-methyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)-ethyl]-amide



5 ESI-MS $[M+H]^+$ = 455

Calculated for $C_{24}H_{30}N_4O_3S$ = 454

Example 7: 1-Methyl-1H-pyrazole-4-sulfonic acid [2-(1-benzyl-2-methyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)-ethyl]-amide



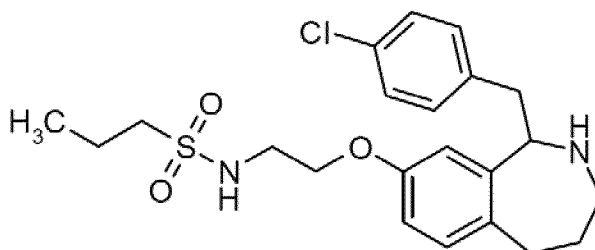
10

ESI-MS $[M+H]^+$ = 455

Calculated for $C_{24}H_{30}N_4O_3S$ = 454

Example 8: Propane-1-sulfonic acid {2-[1-(4-chlorobenzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy]-ethyl}-amide

15

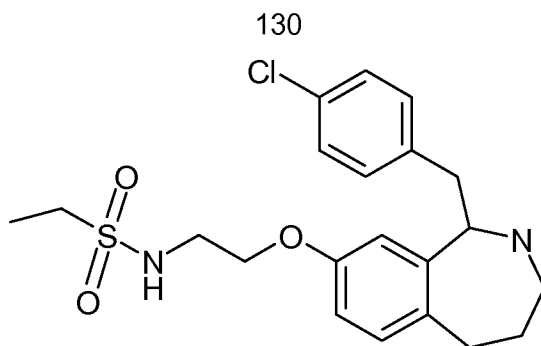


ESI-MS $[M+H]^+$ = 437

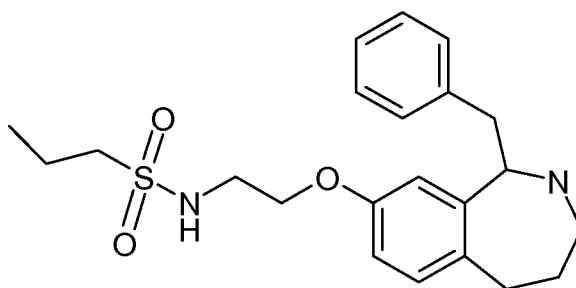
Calculated for $C_{22}H_{29}ClN_2O_3S$ = 437

20

Example 9: Ethanesulfonic acid {2-[1-(4-chlorobenzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy]-ethyl}-amide

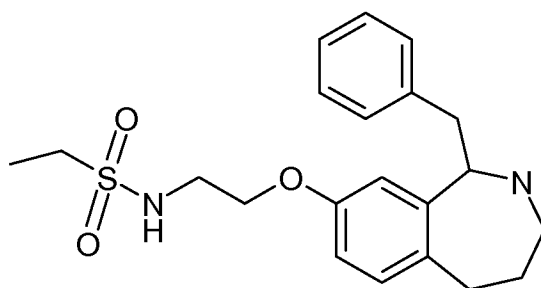
ESI-MS $[M+H]^+$ = 423Calculated for $C_{21}H_{27}ClN_2O_3S$ = 423

- 5 Example 10: Propane-1-sulfonic acid [2-(1-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)-ethyl]-amide

ESI-MS $[M+H]^+$ = 403Calculated for $C_{22}H_{30}N_2O_3S$ = 403

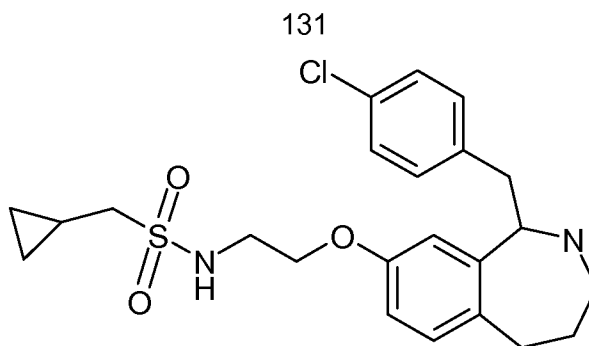
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- Example 11: Ethanesulfonic acid [2-(1-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)-ethyl]-amide

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

15

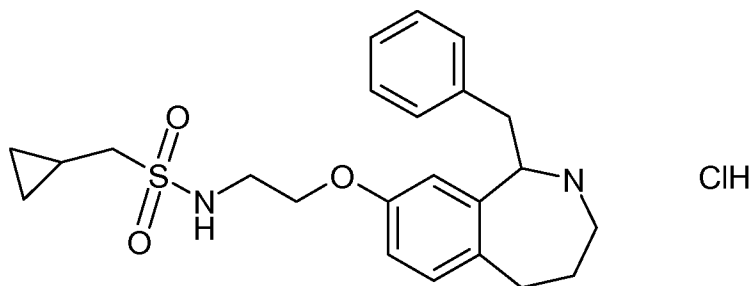
- Example 12: N-{2-[1-(4-Chlorobenzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy]-ethyl}-C-cyclopropyl-methanesulfonamide



The 1R- and 1S-enantiomers have been prepared but the absolute configuration has not been assigned to the individual compounds.

5 ESI-MS $[M+H]^+$ = 449/451 Calculated for $C_{23}H_{29}ClN_2O_3S$ = 449

Example 13: N-{2-[1-Benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy]-ethyl}-C-cyclopropyl-methanesulfonamide

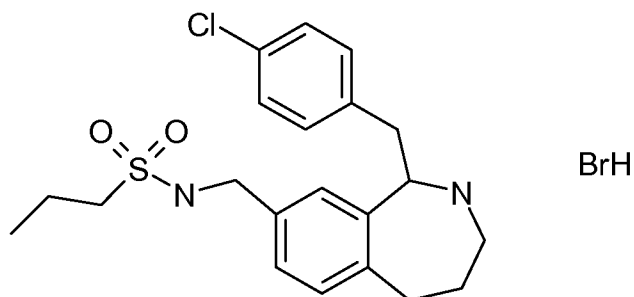


10

The 1R- and 1S-enantiomers have been prepared but the absolute configuration has not been assigned to the individual compounds.

15 ESI-MS $[M+H]^+$ = Calculated for $C_{23}H_{30}N_2O_3S$ = 415

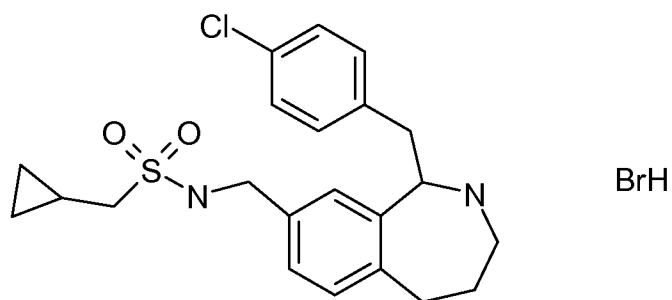
Example 14: Propane-1-sulfonic acid [1-(4-chloro-benzyl)-2,3,4,5-tetra-hydro-1H-benzo[c]azepin-8-ylmethyl]-amide



20

ESI-MS $[M+H]^+$ = 407 Calculated for $C_{21}H_{27}ClN_2O_2S$ = 407

Example 15: N-[1-(4-Chloro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl]-C-cyclopropyl-methanesulfonamide

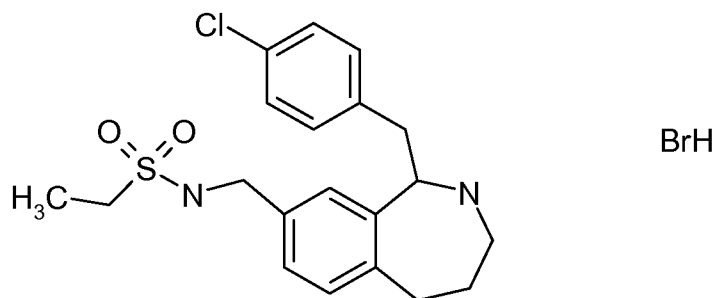


5

ESI-MS $[M+H^+] = 419$ Calculated for $C_{22}H_{27}ClN_2O_2S = 419$

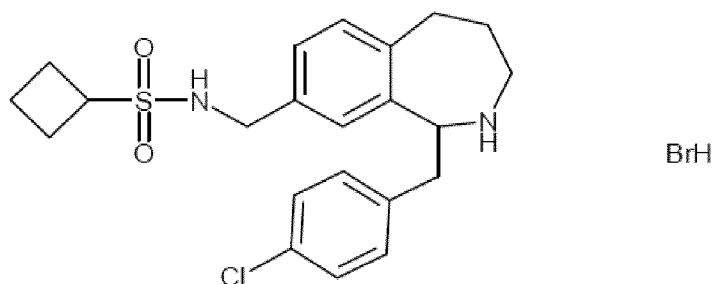
Example 16: Ethanesulfonic acid [1-(4-chloro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl]-amide

10

ESI-MS $[M+H^+] = 393$ Calculated for $C_{20}H_{25}ClN_2O_2S = 393$

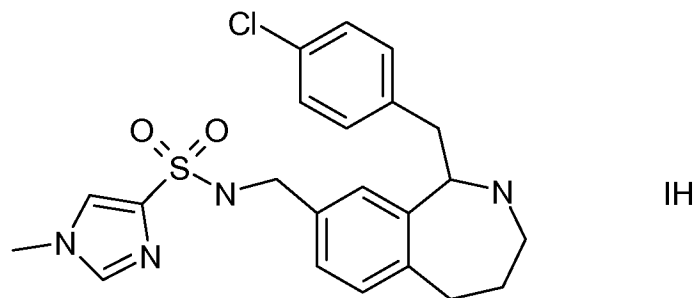
Example 17: Cyclobutanesulfonic acid [1-(4-chloro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl]-amide

15

ESI-MS $[M+H^+] = 419$ Calculated for $C_{22}H_{27}ClN_2O_2S = 419$

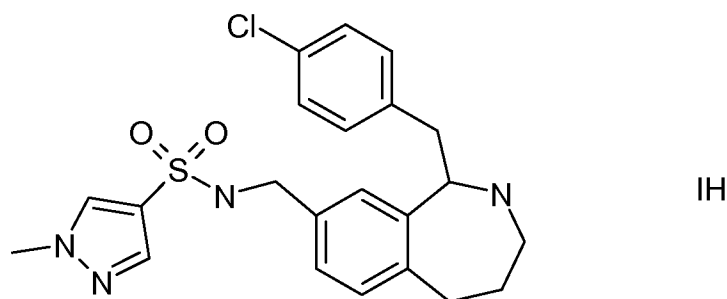
133

Example 18: 1-Methyl-1H-imidazole-4-sulfonic acid [1-(4-chloro-benzyl)-2,3,4,5-tetrahydro-1H-benzo-[c]azepin-8-ylmethyl]-amide

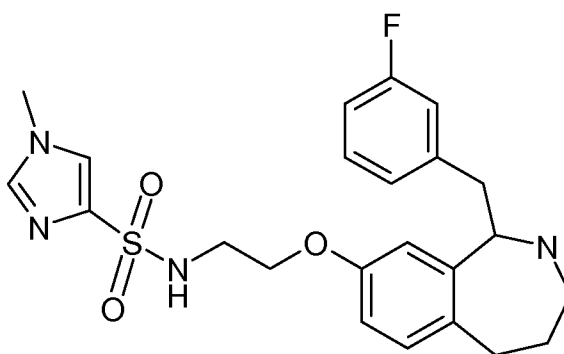
ESI-MS $[M+H]^+$ = 445Calculated for $C_{22}H_{25}ClN_4O_2S$ = 445

5

Example 19: 1-Methyl-1H-pyrazole-4-sulfonic acid [1-(4-chloro-benzyl)-2,3,4,5-tetrahydro-1H-benzo-[c]azepin-8-ylmethyl]-amide

10 ESI-MS $[M+H]^+$ = 445Calculated for $C_{22}H_{25}ClN_4O_2S$ = 445

Example 20: 1-Methyl-1H-imidazole-4-sulfonic acid {2-[1-(3-fluoro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy]-ethyl}-amide



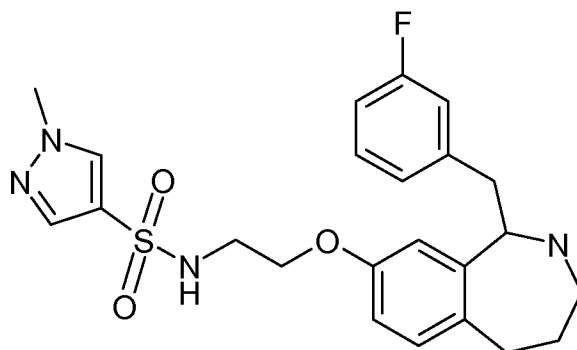
15

ESI-MS $[M+H]^+$ = 459Calculated for $C_{23}H_{27}FN_4O_3S$ = 458

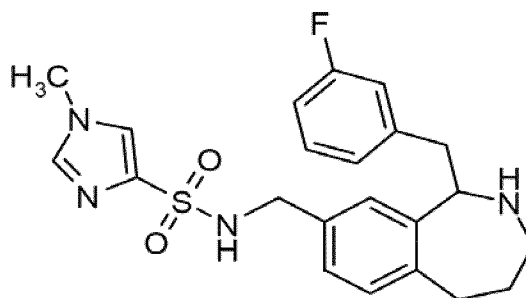
Example 21: 1-Methyl-1H-pyrazole-4-sulfonic acid {2-[1-(3-fluoro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy]-ethyl}-amide

20

134

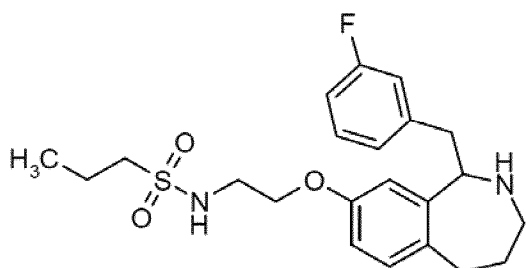
ESI-MS $[M+H^+] = 459$ Calculated for $C_{23}H_{27}FN_4O_3S = 458$

- 5 Example 22: 1-Methyl-1H-imidazole-4-sulfonic acid [1-(3-fluoro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl]-amide

ESI-MS $[M+H^+] = 429$ Calculated for $C_{22}H_{25}FN_4O_2S = 428$

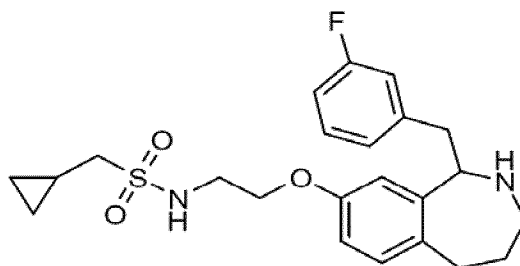
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- Example 23: Propane-1-sulfonic acid {2-[1-(3-fluoro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy]-ethyl}-amide

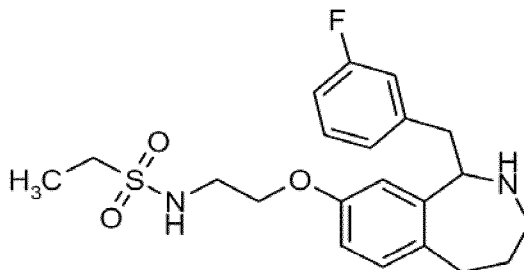
15 ESI-MS $[M+H^+] = 421$ Calculated for $C_{22}H_{29}FN_2O_3S = 421$

- Example 24: C-Cyclopropyl-N-{2-[1-(3-fluoro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy]-ethyl}-methanesulfonamide

135

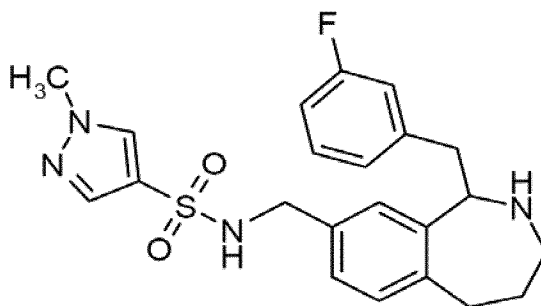
ESI-MS $[M+H^+] = 432$ Calculated for $C_{23}H_{29}FN_2O_3S = 432$

- 5 Example 25: Ethanesulfonic acid {2-[1-(3-fluoro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy]-ethyl}-amide

ESI-MS $[M+H^+] = 407$ Calculated for $C_{21}H_{27}FN_2O_3S = 407$

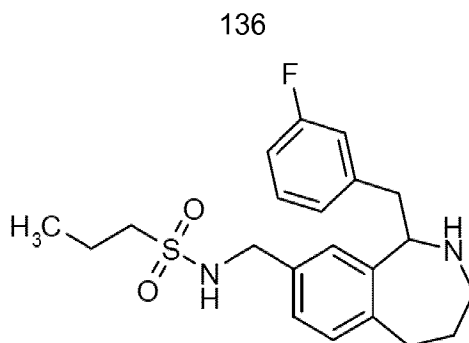
10

- Example 26: 1-Methyl-1H-pyrazole-4-sulfonic acid [1-(3-fluoro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl]-amide

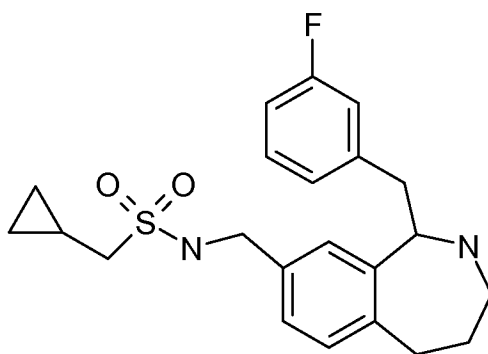
ESI-MS $[M+H^+] = 429$ Calculated for $C_{22}H_{25}FN_4O_2S = 428$

15

- Example 27: Propane-1-sulfonic acid [1-(3-fluoro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl]-amide

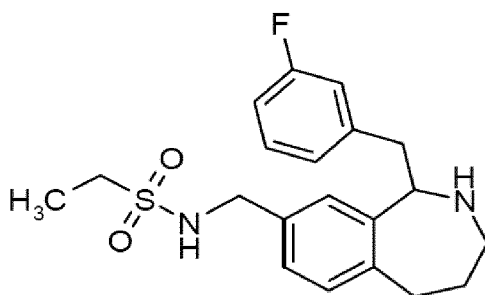
ESI-MS $[M+H]^+$ = 391Calculated for $C_{21}H_{27}FN_2O_2S$ = 390

- 5 Example 28: C-Cyclopropyl-N-[1-(3-fluoro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl]-methanesulfonamide

ESI-MS $[M+H]^+$ = 403Calculated for $C_{22}H_{27}FN_2O_2S$ = 403

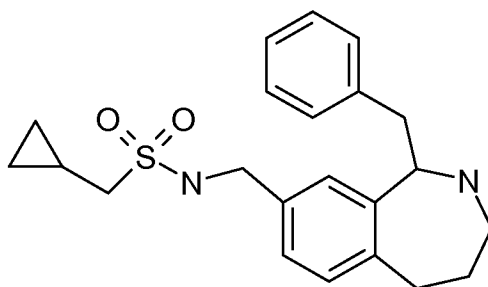
10

- Example 29: Ethanesulfonic acid [1-(3-fluoro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl]-amide

15 ESI-MS $[M+H]^+$ = 377Calculated for $C_{20}H_{25}FN_2O_2S$ = 376

137

Example 30: N-(1-Benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-C-cyclopropyl-methane-sulfonamide

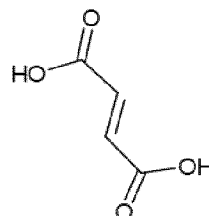
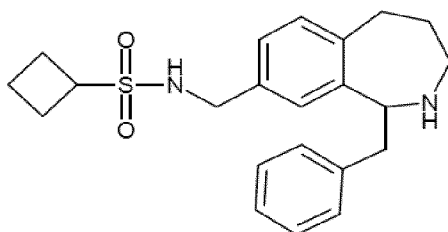


ClH

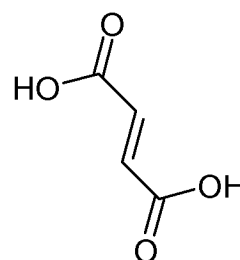
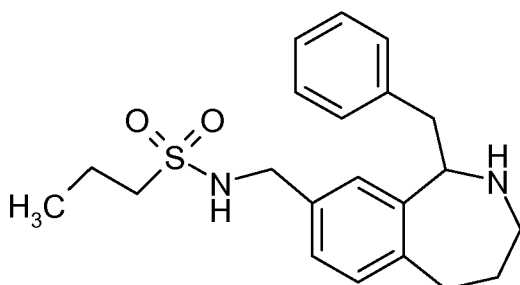
ESI-MS $[M+H^+] = 385$ Calculated for $C_{22}H_{28}N_2O_2S = 385$

5

Example 31: Cyclobutanesulfonic acid (1-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-amide; compound with (E)-buten-2-enedioic acid

10 ESI-MS $[M+H^+] = 395$ Calculated for $C_{22}H_{28}N_2O_2S = 385$

Example 32: Propane-1-sulfonic acid (1-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]-azepin-8-ylmethyl)-amide; compound with (E)-buten-2-enedioic acid



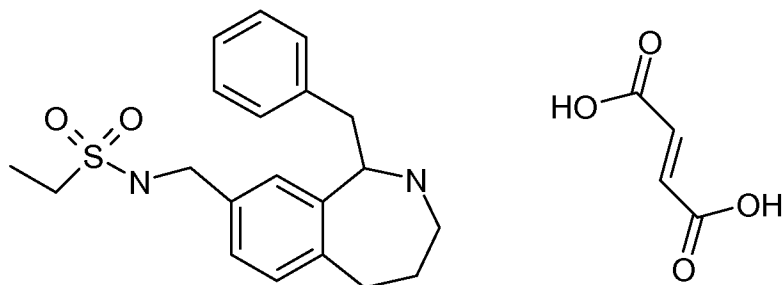
15

ESI-MS $[M+H^+] = 373$ Calculated for $C_{21}H_{28}N_2O_2S = 373$

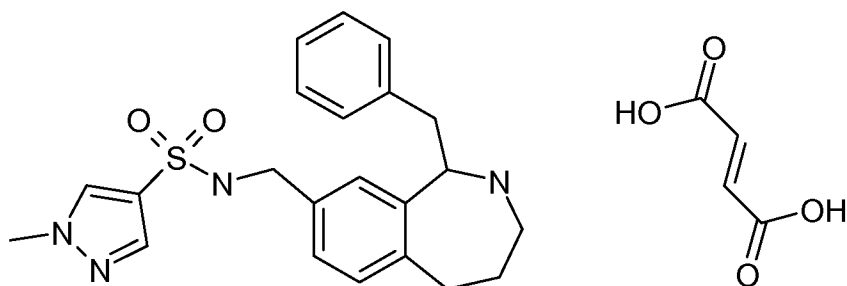
Example 33: Ethanesulfonic acid (1-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]-azepin-8-ylmethyl)-amide; compound with (E)-buten-2-enedioic acid

20

138

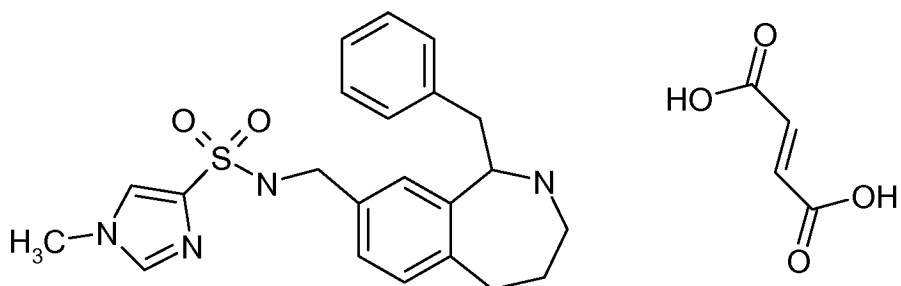
ESI-MS $[M+H]^+$ = 359Calculated for $C_{20}H_{26}N_2O_2S$ = 358

- 5 Example 34: 1-Methyl-1H-pyrazole-4-sulfonic acid (1-benzyl-2,3,4,5-tetra-hydro-1H-benzo[c]azepin-8-ylmethyl)-amide; compound with (E)-buten-2-enedioic acid

ESI-MS $[M+H]^+$ = 411Calculated for $C_{22}H_{26}N_4O_3S$ = 411

10

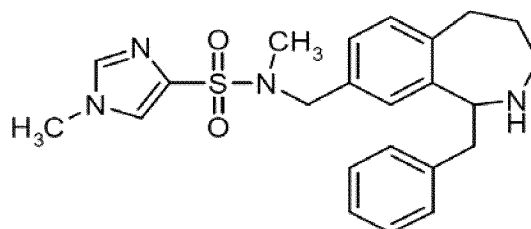
- Example 35: 1-Methyl-1H-imidazole-4-sulfonic acid (1-benzyl-2,3,4,5-tetra-hydro-1H-benzo[c]azepin-8-ylmethyl)-amide; compound with (E)-buten-2-enedioic acid

15 ESI-MS $[M+H]^+$ = 411Calculated for $C_{22}H_{26}N_4O_3S$ = 411

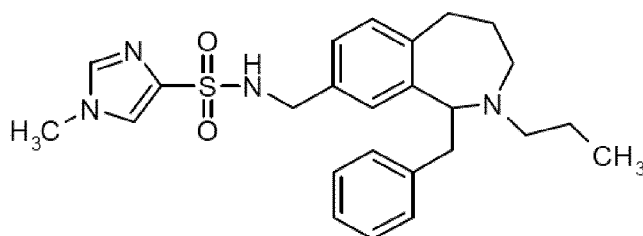
- Example 36: 1-Methyl-1H-imidazole-4-sulfonic acid (1-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-methyl-amide

20

139

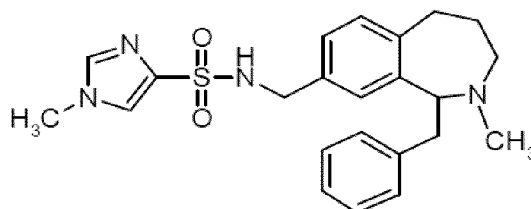
ESI-MS $[M+H]^+$ = 425Calculated for $C_{23}H_{28}N_4O_2S$ = 425

- 5 Example 37: 1-Methyl-1H-imidazole-4-sulfonic acid (1-benzyl-2-propyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-amide

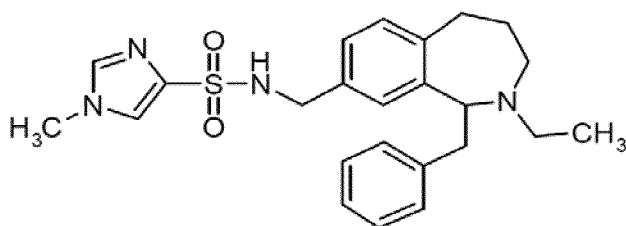
ESI-MS $[M+H]^+$ = 453Calculated for $C_{25}H_{32}N_4O_2S$ = 453

10

- Example 38: 1-Methyl-1H-imidazole-4-sulfonic acid (1-benzyl-2-methyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-amide

15 ESI-MS $[M+H]^+$ = 425Calculated for $C_{23}H_{28}N_4O_2S$ = 425

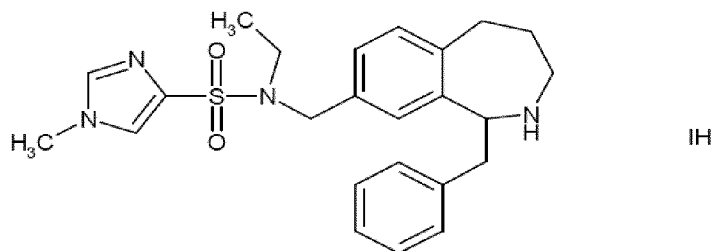
- Example 39: 1-Methyl-1H-imidazole-4-sulfonic acid (1-benzyl-2-ethyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-amide



20

ESI-MS $[M+H]^+$ = 439Calculated for $C_{24}H_{30}N_4O_2S$ = 439

Example 40: 1-Methyl-1H-imidazole-4-sulfonic acid (1-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-ethyl-amide

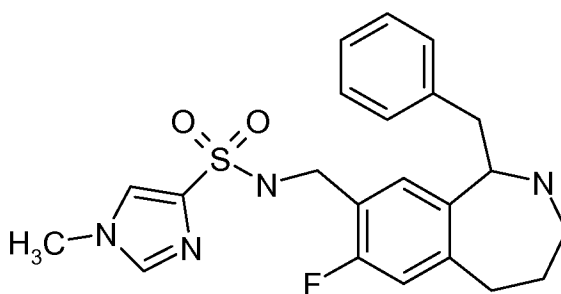


5

ESI-MS $[M+H^+] = 439$ Calculated for $C_{24}H_{30}N_4O_2S = 439$

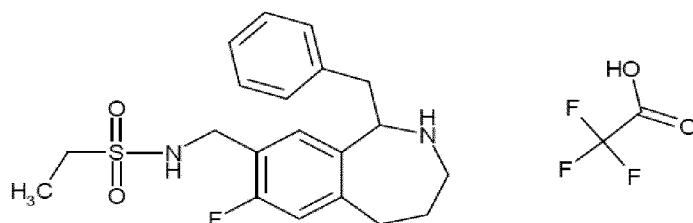
Example 41: 1-Methyl-1H-imidazole-4-sulfonic acid (1-benzyl-7-fluoro-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-amide

10

ESI-MS $[M+H^+] = 429$ Calculated for $C_{22}H_{25}FN_4O_2S = 428$

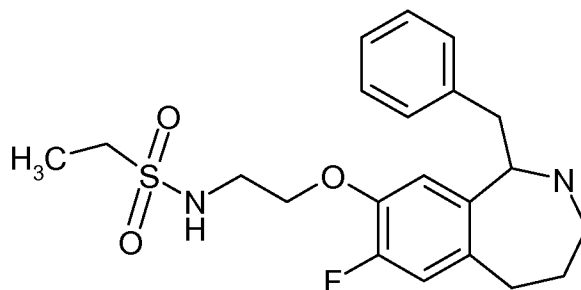
Example 42: Ethanesulfonic acid (1-benzyl-7-fluoro-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-amide; compound with trifluoro-acetic acid

15

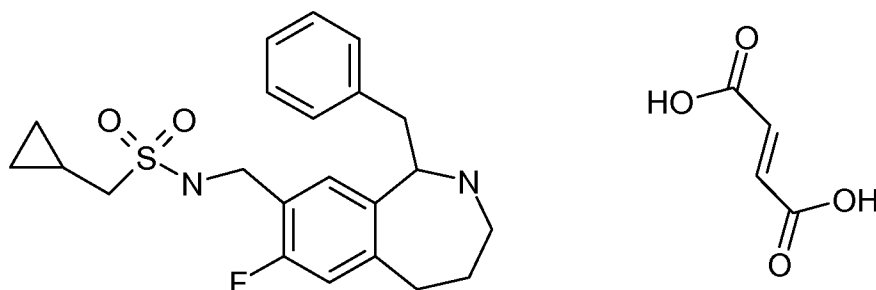
20 ESI-MS $[M+H^+] = 354$ Calculated for $C_{20}H_{25}FN_2O_2S = 376$

Example 43: Ethanesulfonic acid [2-(1-benzyl-7-fluoro-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)-ethyl]-amide

141

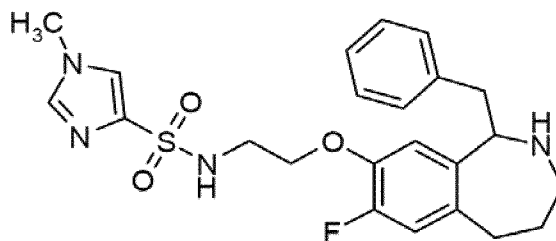
ESI-MS $[M+H]^+$ = 407Calculated for $C_{21}H_{27}FN_2O_3S$ = 406

- 5 Example 44: N-(1-Benzyl-7-fluoro-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-C-cyclopropyl-methanesulfonamide; compound with (E)-but-2-enedioic acid

ESI-MS $[M+H]^+$ = 403Calculated for $C_{22}H_{27}FN_2O_2S$ = 403

10

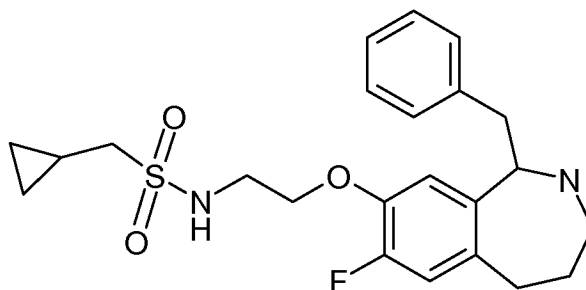
- Example 45: 1-Methyl-1H-imidazole-4-sulfonic acid [2-(1-benzyl-7-fluoro-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)-ethyl]-amide

ESI-MS $[M+H]^+$ = 459Calculated for $C_{23}H_{27}FN_4O_3S$ = 459

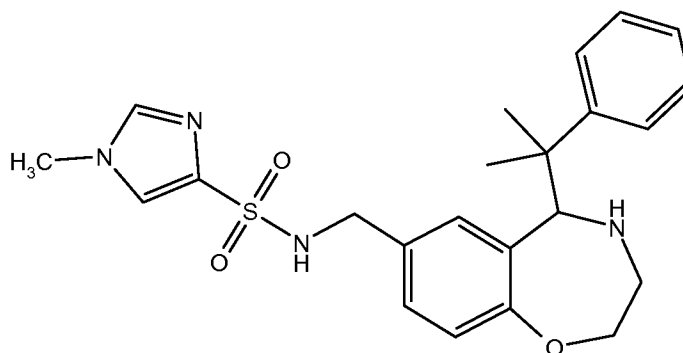
15

- Example 46: N-[2-(1-Benzyl-7-fluoro-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)-ethyl]-C-cyclopropyl-methanesulfonamide

142

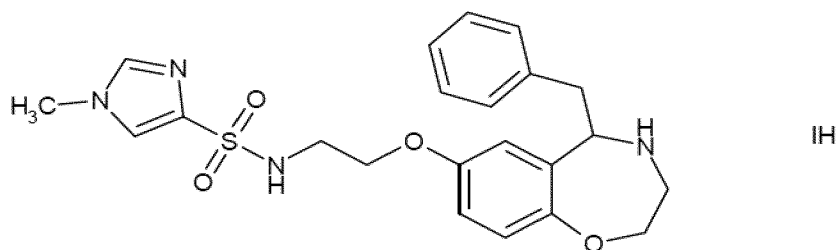
ESI-MS $[M+H]^+$ = 433Calculated for $C_{23}H_{29}FN_2O_3S$ =

Example 47: 1-Methyl-1H-imidazole-4-sulfonic acid [5-(1-methyl-1-phenyl-ethyl)-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepin-7-ylmethyl]-amide

ESI-MS $[M+H]^+$ = 440Calculated for $C_{23}H_{28}N_4O_3S$ = 441

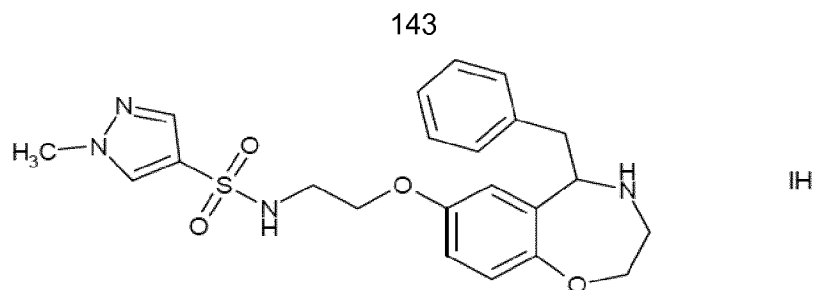
10

Example 48: 1-Methyl-1H-imidazole-4-sulfonic acid [2-(5-benzyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepin-7-yloxy)-ethyl]-amide

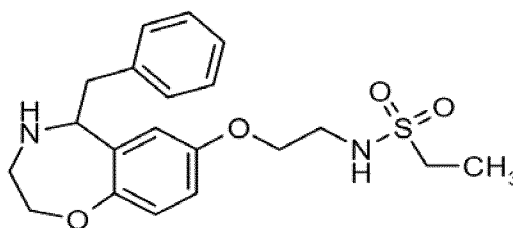
ESI-MS $[M+H]^+$ = 443Calculated for $C_{22}H_{26}N_4O_4S$ = 444

15

Example 49: 1-Methyl-1H-pyrazole-4-sulfonic acid [2-(5-benzyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepin-7-yloxy)-ethyl]-amide

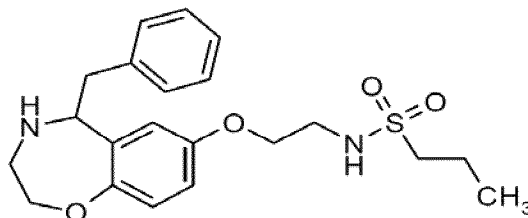
ESI-MS $[M+H^+] = 443$ Calculated for $C_{22}H_{26}N_4O_4S = 444$

- 5 Example 50: Ethanesulfonic acid [2-(5-benzyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepin-7-yloxy)-ethyl]-amide

ESI-MS $[M+H^+] = 391$ Calculated for $C_{20}H_{26}N_2O_4S = 390$

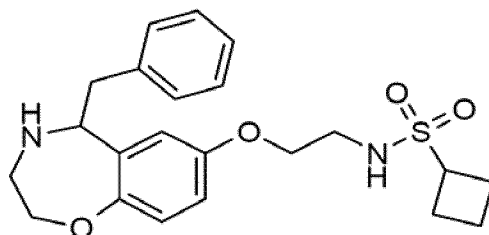
10

- Example 51: Propane-1-sulfonic acid [2-(5-benzyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepin-7-yloxy)-ethyl]-amide

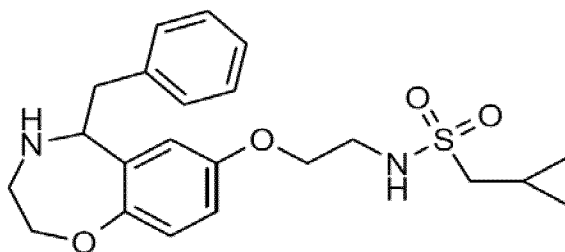
ESI-MS $[M+H^+] = 405$ Calculated for $C_{21}H_{28}N_2O_4S = 404$

15

- Example 52: Cyclobutanesulfonic acid [2-(5-benzyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepin-7-yloxy)-ethyl]-amide

20 ESI-MS $[M+H^+] = 417$ Calculated for $C_{22}H_{28}N_2O_4S = 417$

Example 53: N-[2-(5-Benzyl-2,3,4,5-tetrahydro-benzo[f][1,4]oxazepin-7-yloxy)-ethyl]-C-cyclopropyl-methanesulfonamide



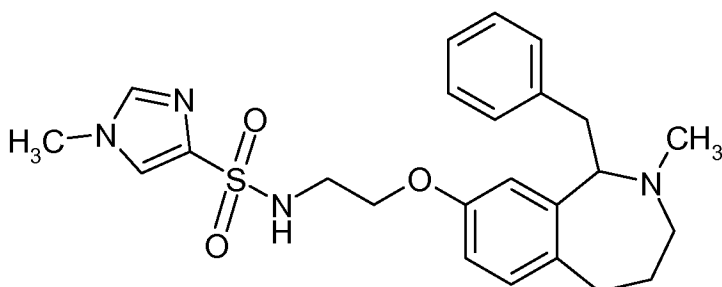
ESI-MS $[M+H]^+ = 417$

Calculated for $C_{22}H_{28}N_2O_4S = 417$

5

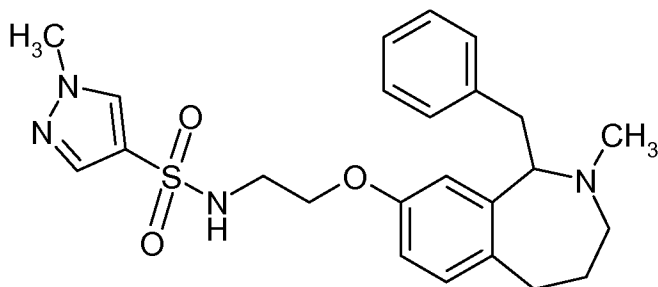
The following compounds were obtained or can be obtained using the procedures described herein.

1



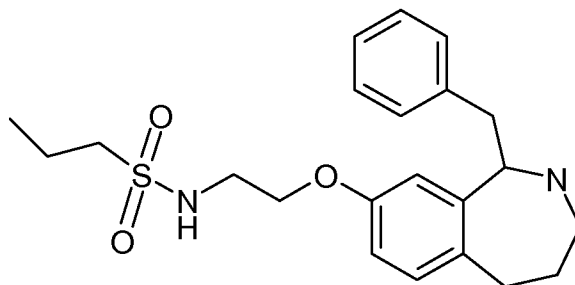
1-Methyl-1H-imidazole-4-sulfonic acid [2-(1-benzyl-2-methyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)-ethyl]-amide

2



1-Methyl-1H-pyrazole-4-sulfonic acid [2-(1-benzyl-2-methyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)-ethyl]-amide

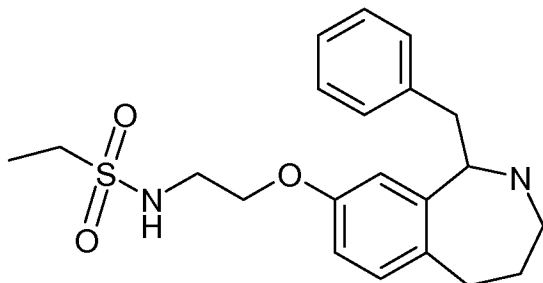
3



Propane-1-sulfonic acid [2-(1-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)-ethyl]-amide

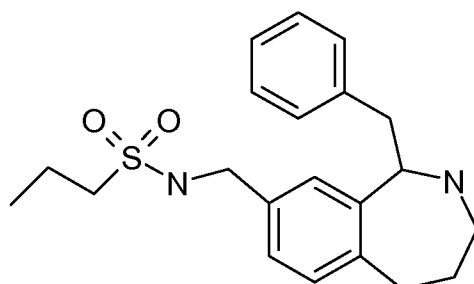
145

4



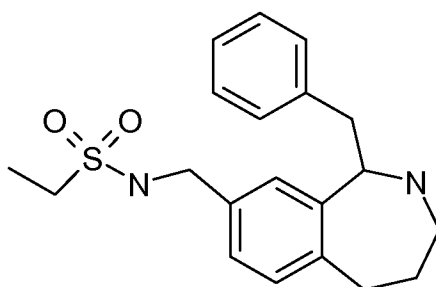
Ethanesulfonic acid [2-(1-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)-ethyl]-amide

5



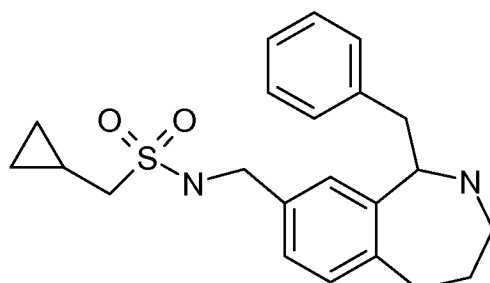
Propane-1-sulfonic acid (1-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]-azepin-8-ylmethyl)-amide

6



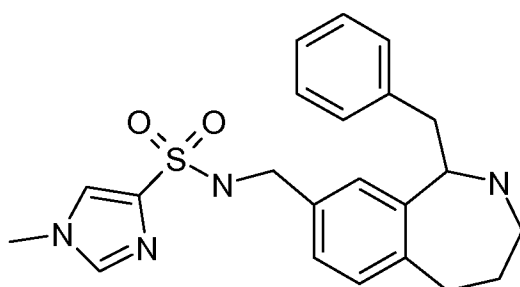
Ethanesulfonic acid (1-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]-azepin-8-ylmethyl)-amide

7



N-(1-Benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-C-cyclopropyl-methanesulfonamide

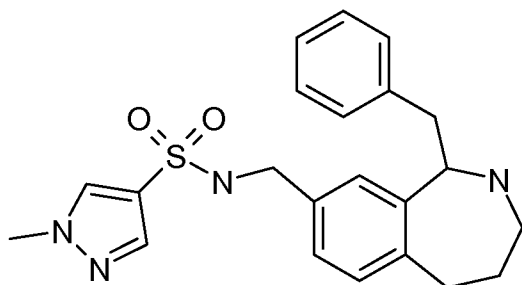
8



1-Methyl-1H-imidazole-4-sulfonic acid (1-benzyl-2,3,4,5-tetra-hydro-1H-benzo[c]azepin-8-ylmethyl)-amide

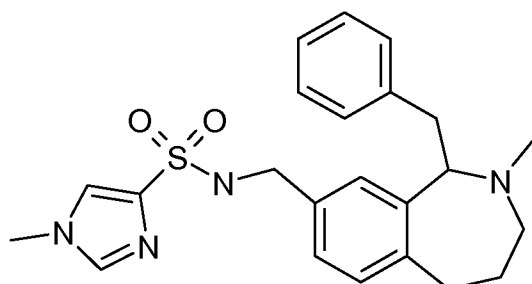
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9



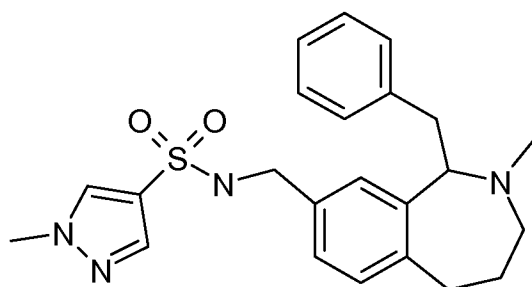
1-Methyl-1H-pyrazole-4-sulfonic acid (1-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-amide

10



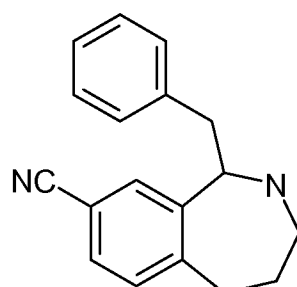
1-Methyl-1H-imidazole-4-sulfonic acid (1-benzyl-2-methyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-amide

11



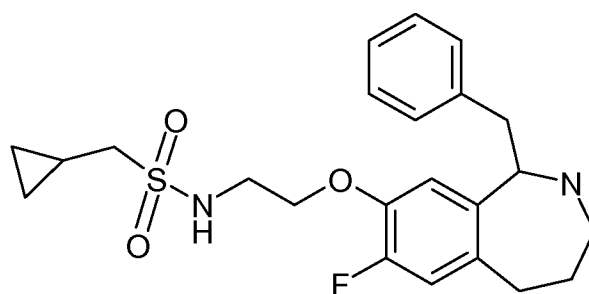
1-Methyl-1H-pyrazole-4-sulfonic acid (1-benzyl-2-methyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-amide

12



1-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepine-8-carbonitrile

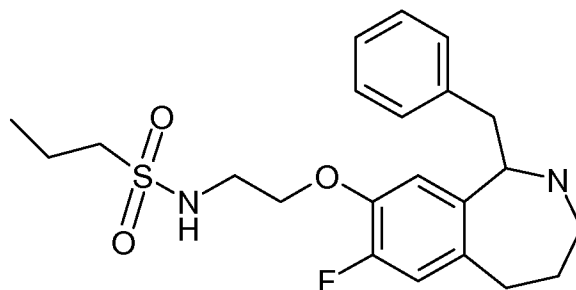
13



N-[2-(1-Benzyl-7-fluoro-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)-ethyl]-C-cyclopropylmethanesulfonamide

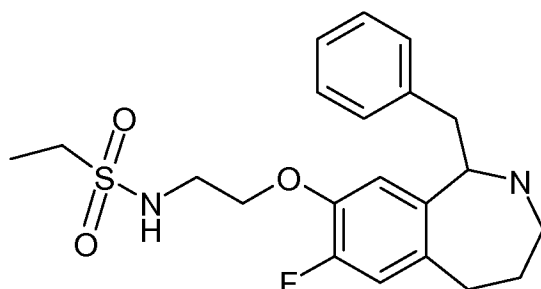
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14



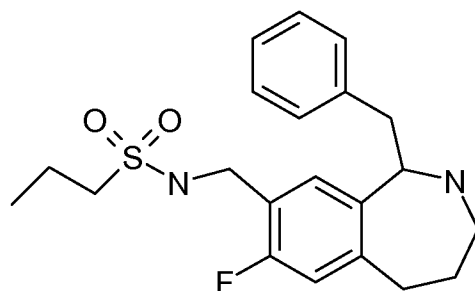
Propane-1-sulfonic acid [2-(1-benzyl-7-fluoro-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)-ethyl]-amide

15



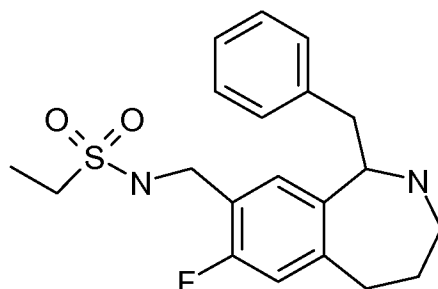
Ethanesulfonic acid [2-(1-benzyl-7-fluoro-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)-ethyl]-amide

16



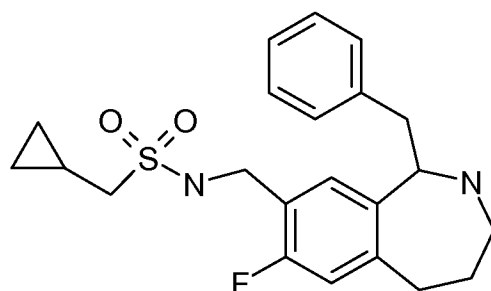
Propane-1-sulfonic acid (1-benzyl-7-fluoro-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-amide

17



Ethanesulfonic acid (1-benzyl-7-fluoro-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-amide

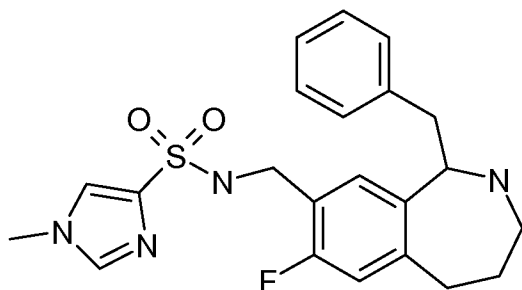
18



N-(1-Benzyl-7-fluoro-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-C-cyclopropylmethanesulfonamide

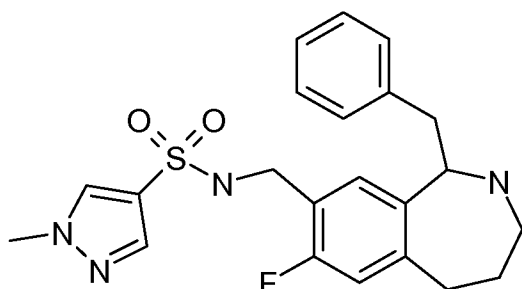
148

19



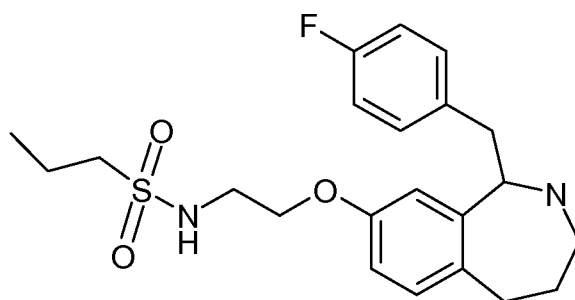
1-Methyl-1H-imidazole-4-sulfonic acid (1-benzyl-7-fluoro-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-amide

20



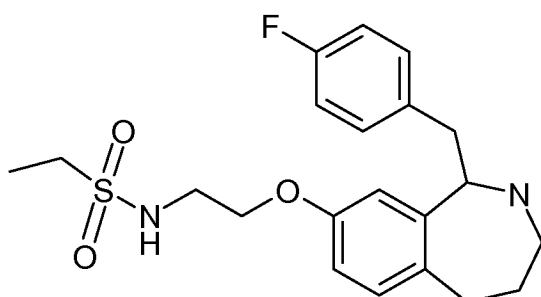
1-Methyl-1H-pyrazole-4-sulfonic acid (1-benzyl-7-fluoro-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-amide

21



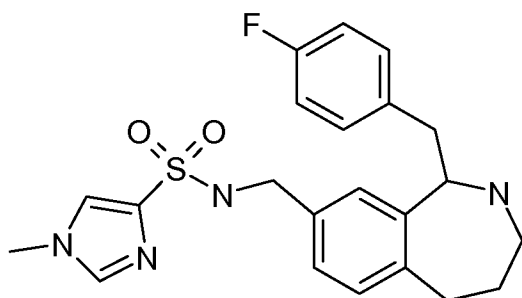
Propane-1-sulfonic acid {2-[1-(4-fluoro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy]-ethyl}-amide

22



Ethanesulfonic acid {2-[1-(4-fluoro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy]-ethyl}-amide

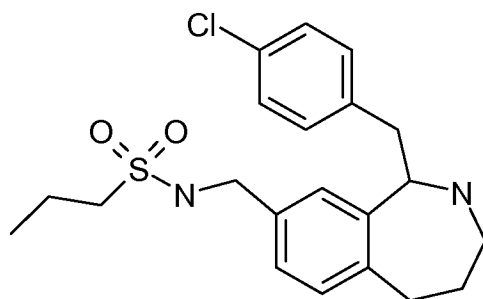
23



1-Methyl-1H-imidazole-4-sulfonic acid [1-(4-fluoro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl]-amide

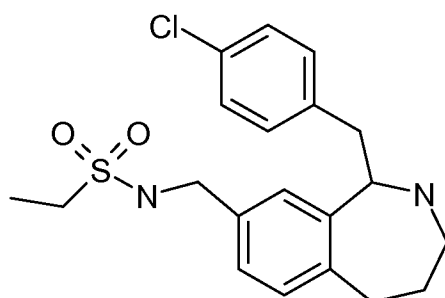
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24



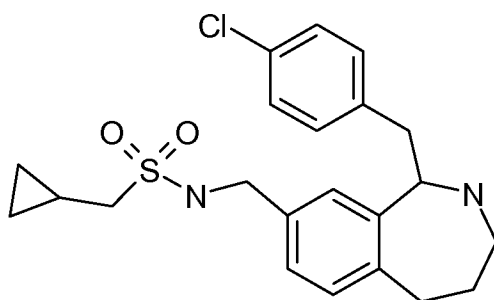
Propane-1-sulfonic acid [1-(4-chloro-benzyl)-2,3,4,5-tetra-hydro-1H-benzo[c]azepin-8-ylmethyl]-amide

25



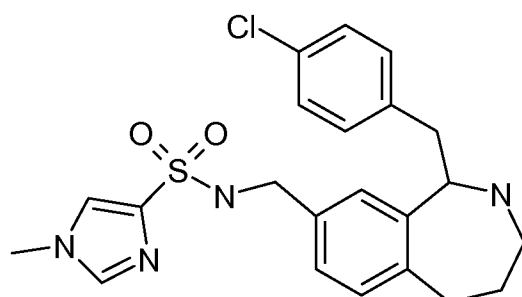
Ethanesulfonic acid [1-(4-chloro-benzyl)-2,3,4,5-tetra-hydro-1H-benzo[c]azepin-8-ylmethyl]-amide

26



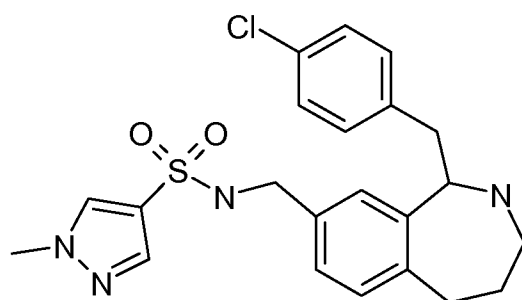
N-[1-(4-Chloro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl]-C-cyclopropyl-methanesulfonamide

27



1-Methyl-1H-imidazole-4-sulfonic acid [1-(4-chloro-benzyl)-2,3,4,5-tetrahydro-1H-benzo-[c]azepin-8-ylmethyl]-amide

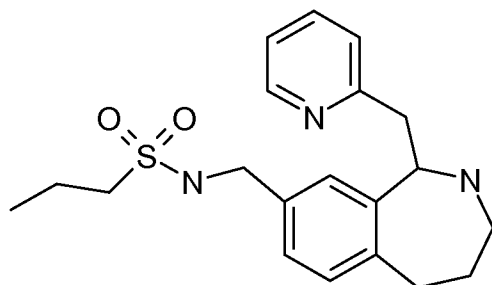
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1-Methyl-1H-pyrazole-4-sulfonic acid [1-(4-chloro-benzyl)-2,3,4,5-tetrahydro-1H-benzo-[c]azepin-8-ylmethyl]-amide

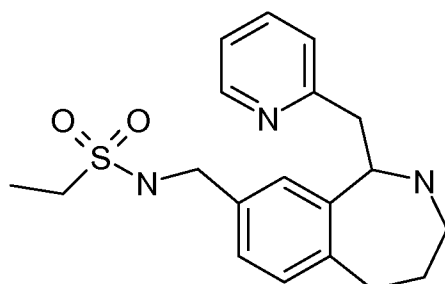
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29



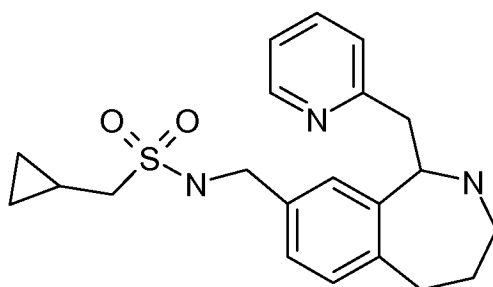
Propane-1-sulfonic acid (1-pyridin-2-yl-methyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-amide

30



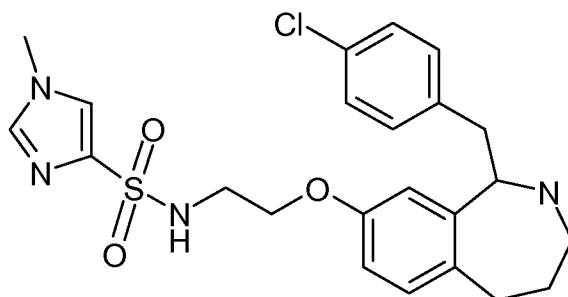
Ethanesulfonic acid (1-pyridin-2-yl-methyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-amide

31



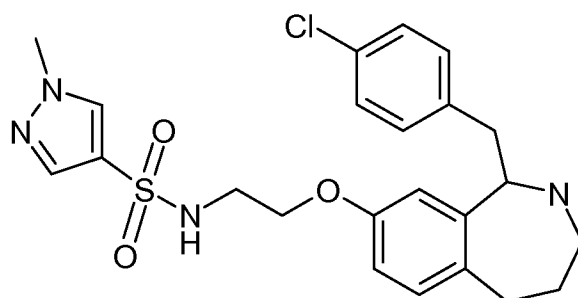
C-Cyclopropyl-N-(1-pyridin-2-ylmethyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-methanesulfonamide

32



1-Methyl-1H-imidazole-4-sulfonic acid {2-[1-(4-chlorobenzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy]-ethyl}-amide

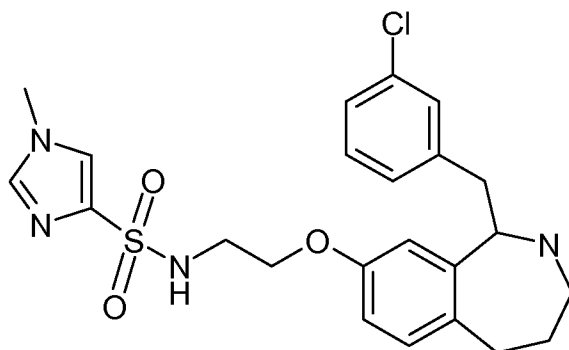
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1-Methyl-1H-pyrazole-4-sulfonic acid {2-[1-(4-chlorobenzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy]-ethyl}-amide

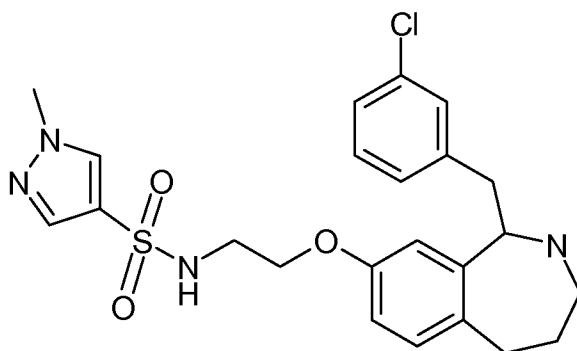
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34



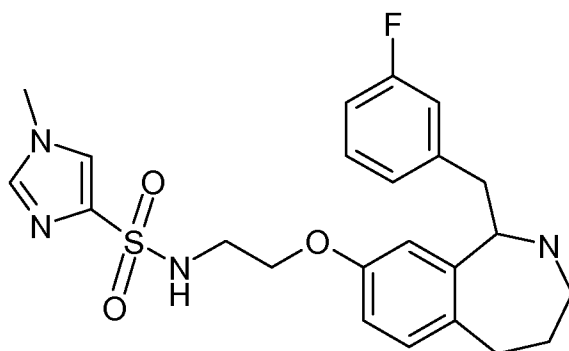
1-Methyl-1H-imidazole-4-sulfonic acid {2-[1-(3-chloro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy]-ethyl}-amide

35



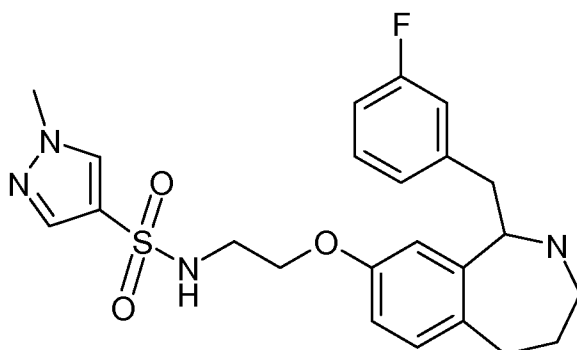
1-Methyl-1H-pyrazole-4-sulfonic acid {2-[1-(3-chloro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy]-ethyl}-amide

36



1-Methyl-1H-imidazole-4-sulfonic acid {2-[1-(3-fluoro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy]-ethyl}-amide

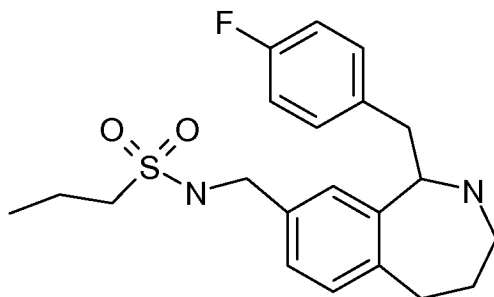
37



1-Methyl-1H-pyrazole-4-sulfonic acid {2-[1-(3-fluoro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy]-ethyl}-amide

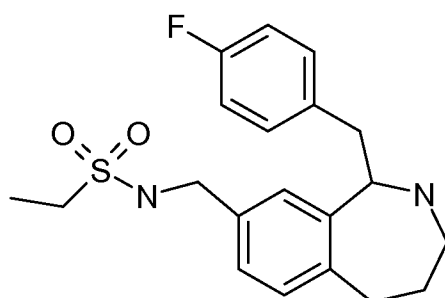
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38



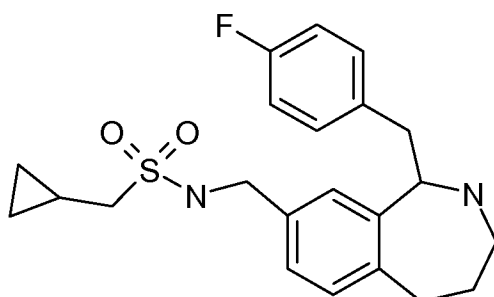
Propane-1-sulfonic acid [1-(4-fluoro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl]-amide

39



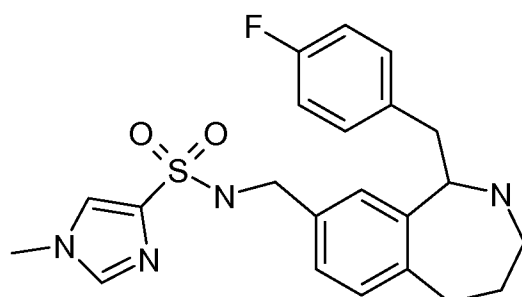
Ethanesulfonic acid [1-(4-fluoro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl]-amide

40



C-Cyclopropyl-N-[1-(4-fluoro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl]-methanesulfonamide

41



1-Methyl-1H-imidazole-4-sulfonic acid [1-(4-fluoro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl]-amide

Biological testing

- 5 1. [³H]-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
- 10 mM L-Alanine (Merck #1007). 80 µl HBSS buffer were added, followed by 10 µl inhibitor or vehicle (10% DMSO) and 10 µl [³H]-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 μ M Org24598. IC₅₀ calculations were made by four-parametric logistic nonlinear regression analysis (GraphPad Prism) using determinations within the range of linear increase of [3H]-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.

3. Metabolic stability

Metabolic stability was determined as follows:

0.5 μ M test substance was preincubated together with human liver microsomes (0.25 mg of microsomal protein/ml) in 0.05 M potassium phosphate buffer of pH 7.4 in microtiter plates at 37°C for 5 min. The reaction was started by adding NADPH (1.0 mM). After 0, 5, 10, 15, 20 and 30 min, 65 μ l aliquots were removed, and the reaction was immediately stopped and cooled with twice the amount of ethanol. The samples were frozen until analyzed. The remaining concentration of undegraded test substance was determined by LC MSMS. The half-life (T_{1/2}) was determined from the gradient of the signal of test substance/unit time plot, allowing to calculate the half-life of the test substance, assuming first order kinetics, from the decrease in the concentration of the compound with time. The microsomal clearance (mCl) was calculated from $mCl = \ln 2 / T_{1/2} / (\text{content of microsomal protein in mg/ml}) \times 1000$ (modified from references: Di, The Society for Biomolecular Screening, 2003, 453-462; Obach, DMD, 1999 vol 27. N 11, 1350-1359).

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

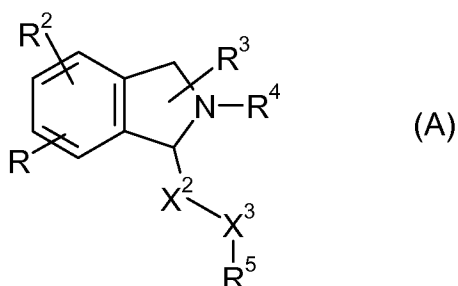
Example	radioligand binding K _{iapp} [nmol]	human mCl [μ l/min/mg]
1	> 10000	$\leq$ 50
2	$\leq$ 100	$\leq$ 50
3	$\leq$ 10	$\leq$ 50
4	$\leq$ 100	$\leq$ 50
5	$\leq$ 10000	$\leq$ 250
6	$\leq$ 10	$\leq$ 150

7	≤ 10	≤ 200
8	≤ 1000	≤ 250
9	≤ 10000	≤ 100
10	≤ 100	≤ 50
11	≤ 1000	≤ 50
12*	≤ 1000	≤ 150
	≤ 10000	≤ 150
13*	≤ 100	≤ 50
	≤ 1000	≤ 50
14	≤ 1000	≤ 50
15	≤ 10000	≤ 100
16	≤ 10000	≤ 50
17	≤ 1000	≤ 100
18	≤ 1000	≤ 50
19	≤ 100	≤ 100
20	≤ 10	≤ 50
21	≤ 10	≤ 100
22	≤ 10	≤ 50
23	≤ 100	≤ 150
24	≤ 100	≤ 100
25	≤ 1000	≤ 50
26	≤ 10	≤ 50
27	≤ 1000	≤ 100
28	≤ 100	≤ 50
29	≤ 1000	≤ 50
30	≤ 100	≤ 50
31	≤ 100	≤ 100
32	≤ 1000	≤ 100
33	≤ 10000	≤ 50
34	≤ 10	≤ 50
35	≤ 10	≤ 50
36	≤ 100	≤ 50
37	≤ 10	≤ 300
38	≤ 100	≤ 100
39	≤ 100	≤ 150
40	≤ 100	≤ 50
41	≤ 10	≤ 50
42	≤ 1000	≤ 50
43	≤ 1000	≤ 50

44	≤ 100	≤ 50
45	≤ 100	≤ 50
46	≤ 100	≤ 50
47	≤ 10000	-
48	≤ 100	≤ 50
49	≤ 100	≤ 50
50	≤ 10000	≤ 50
51	≤ 1000	≤ 100
52	≤ 1000	≤ 100
53	≤ 1000	≤ 100

* (1R)/(1S)

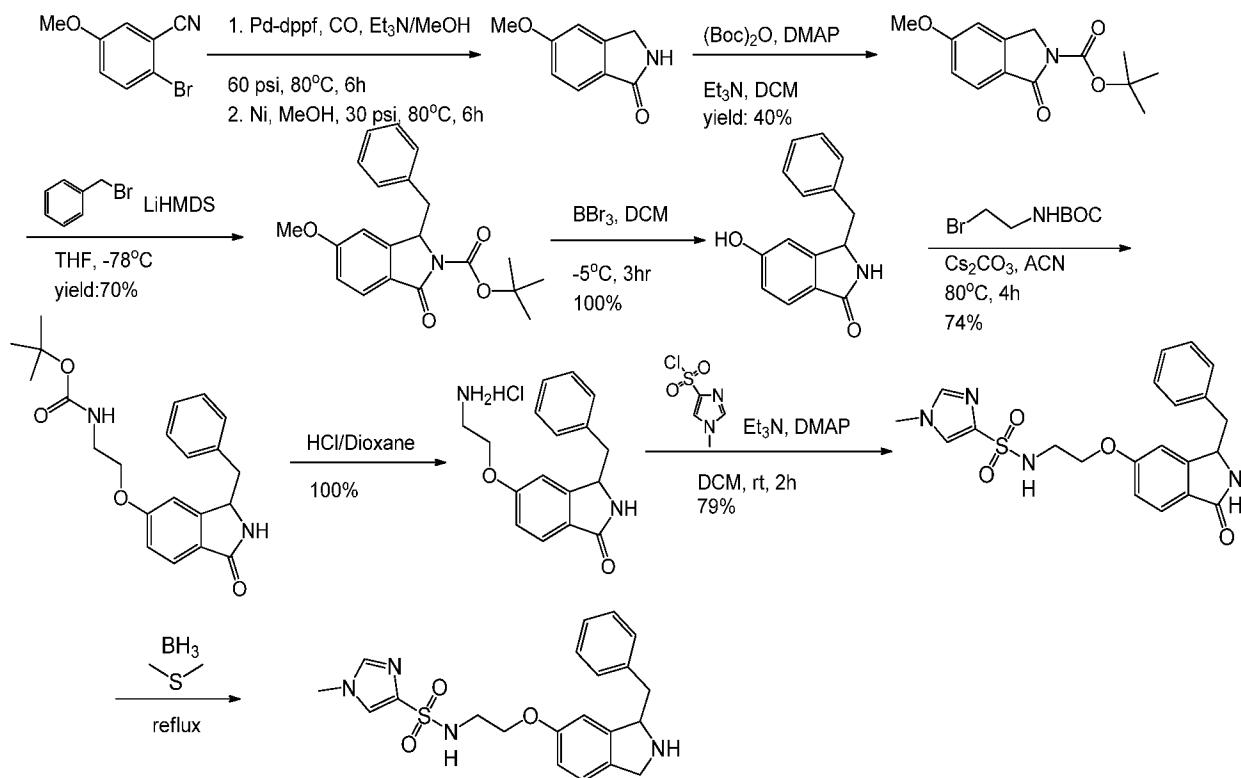
Further, the present application relates to isoindoline derivatives of the formula (A):



wherein R, R², R³, R⁴, X², X³, R⁵ are as defined herein for the benzazepine derivatives, or a physiologically tolerated salt thereof; pharmaceutical compositions comprising such compounds; and the use of such compounds for therapeutic purposes. The compounds are GlyT1 inhibitors.

The isoindoline derivatives and their physiologically tolerated salts can be prepared by analogy to methods which are well known in the art. Suitable methods for the preparation of isoindoline derivatives of formula (A) are outlined in the following schemes.

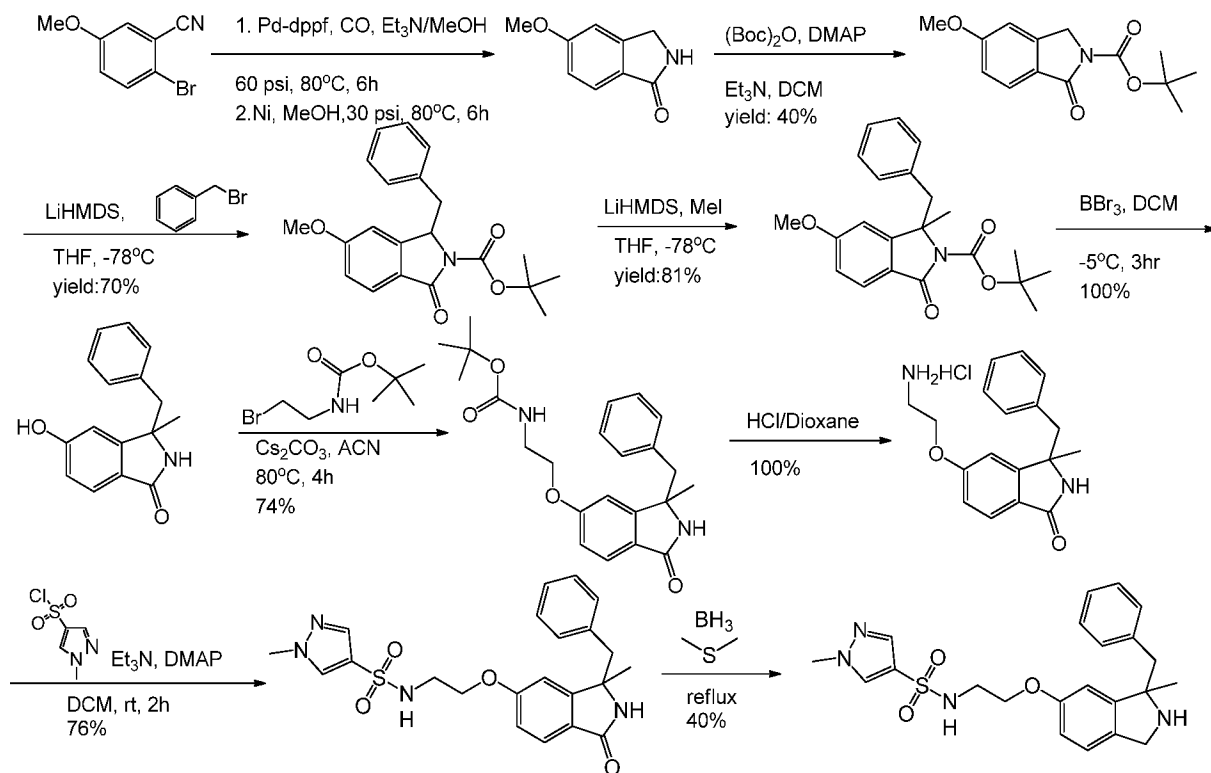
Scheme 1.



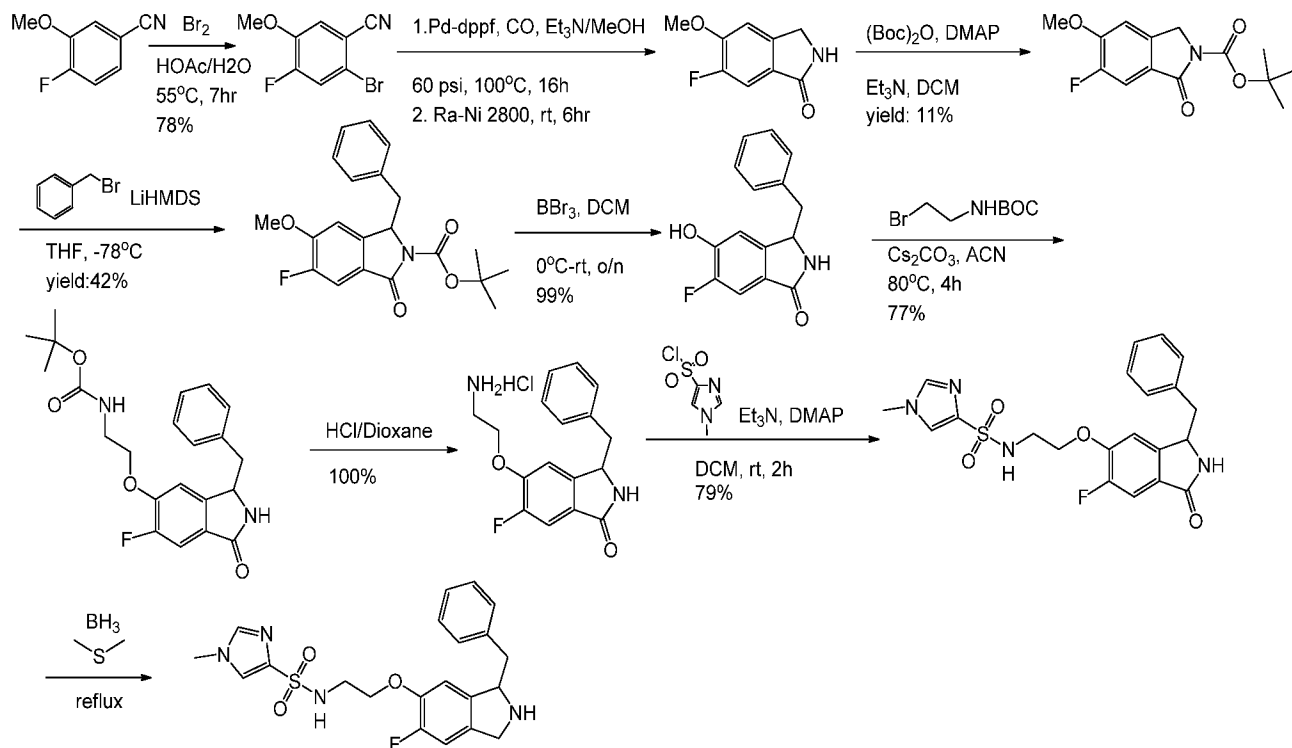
15

Scheme 2.

157



Scheme 3.



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

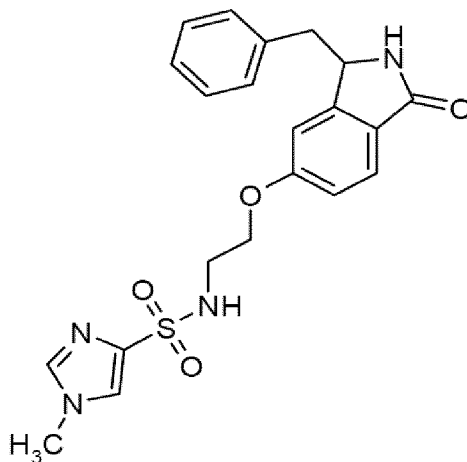
The compounds were characterized by mass spectrometry, generally recorded via HPLC-MS in a fast gradient on C18-material (electrospray-ionisation (ESI) mode).

Preparation Examples

5

The following compounds were obtained using the procedures described herein.

Example A1: N-[2-(3-benzyl-1-oxo-isoindolin-5-yl)oxyethyl]-1-methyl-imidazole-4-sulfonamide



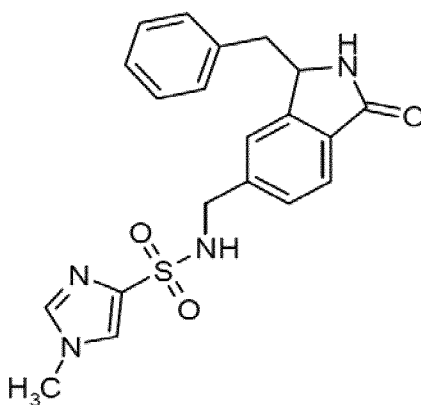
10

ESI-MS $[M+H^+] = 427$

Calculated for $C_{21}H_{22}N_4O_4S = 426$

Example A2: N-[(3-benzyl-1-oxo-isoindolin-5-yl)methyl]-1-methyl-imidazole-4-sulfonamide

15



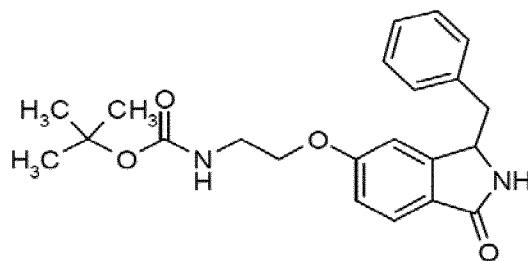
ESI-MS $[M+H^+] = 397$

Calculated for $C_{20}H_{20}N_4O_3S = 396$

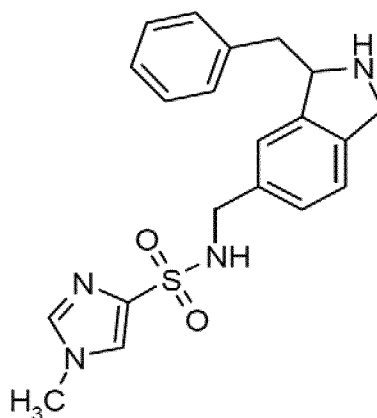
Example A3: [2-(3-Benzyl-1-oxo-2,3-dihydro-1H-isoindol-5-yloxy)-ethyl]-carbamic acid tert-butyl ester

20

159

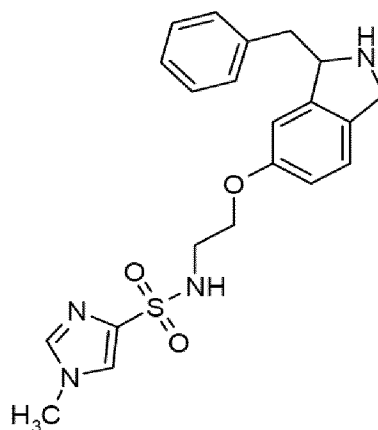
ESI-MS $[M+H]^+ = 383$ Calculated for $C_{22}H_{26}N_2O_4 = 382$

5 Example A4: N-[(3-benzylisoindolin-5-yl)methyl]-1-methyl-imidazole-4-sulfonamide

ESI-MS $[M+H]^+ = 383$ Calculated for $C_{20}H_{22}N_4O_2S = 382$

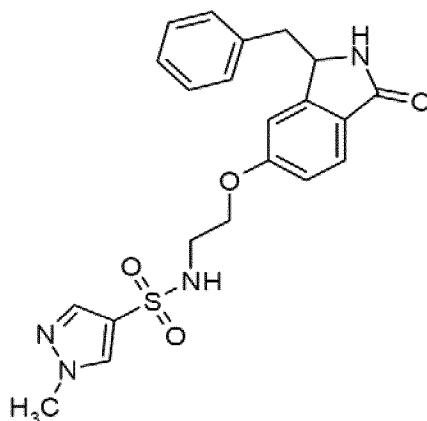
10

Example A5: N-[2-(3-benzylisoindolin-5-yl)oxyethyl]-1-methyl-imidazole-4-sulfonamide

15 ESI-MS $[M+H]^+ = 413$ Calculated for $C_{21}H_{24}N_4O_3S = 412$

160

Example A6: N-[2-(3-benzyl-1-oxo-isindolin-5-yl)oxyethyl]-1-methyl-pyrazole-4-sulfonamide

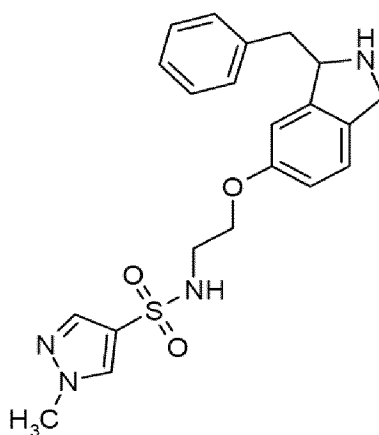


ESI-MS $[M+H]^+$ = 427

Calculated for $C_{21}H_{22}N_4O_4S$ = 426

5

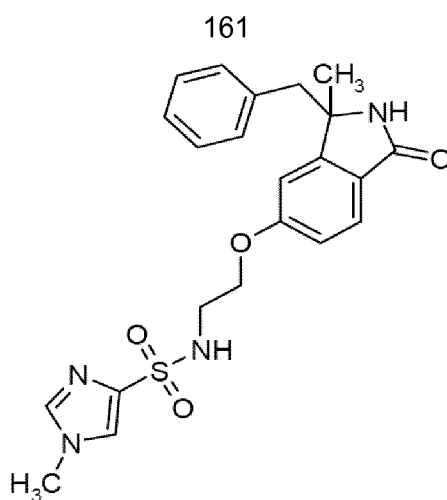
Example A7: N-[2-(3-benzylisindolin-5-yl)oxyethyl]-1-methyl-pyrazole-4-sulfonamide



10 ESI-MS $[M+H]^+$ = 413

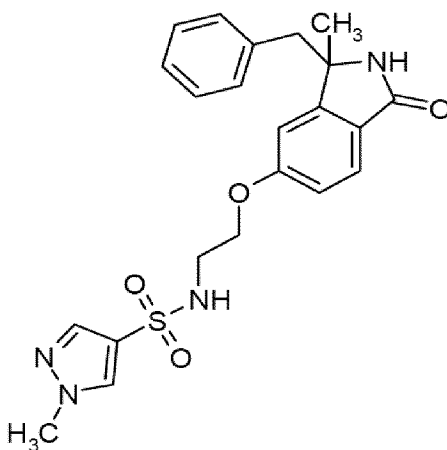
Calculated for $C_{21}H_{24}N_4O_3S$ = 412

Example A8: N-[2-(3-benzyl-3-methyl-1-oxo-isindolin-5-yl)oxyethyl]-1-methyl-imidazole-4-sulfonamide

ESI-MS $[M+H^+] = 441$ Calculated for $C_{22}H_{24}N_4O_4S = 440$

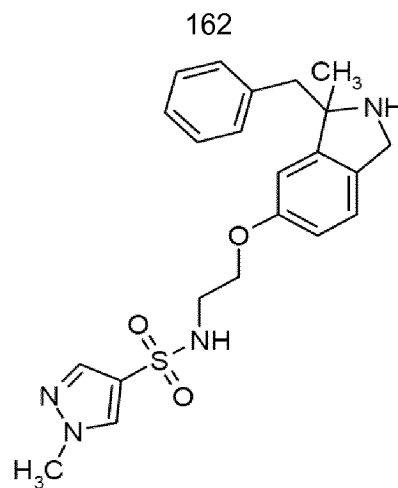
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Example A9: N-[2-(3-benzyl-3-methyl-1-oxo-isoindolin-5-yl)oxyethyl]-1-methyl-pyrazole-4-sulfonamide

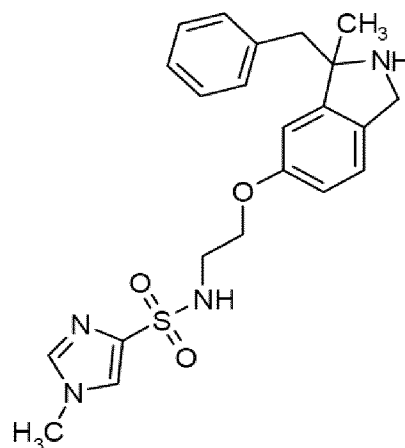
ESI-MS $[M+H^+] = 441$ Calculated for $C_{22}H_{24}N_4O_4S = 440$

10

Example A10: N-[2-(3-benzyl-3-methyl-isoindolin-5-yl)oxyethyl]-1-methyl-pyrazole-4-sulfonamide

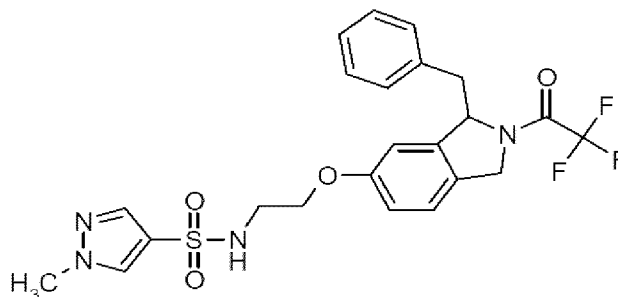
ESI-MS $[M+H]^+ = 427$ Calculated for $C_{22}H_{26}N_4O_3S = 426$

- 5 Example A11: N-[2-(3-benzyl-3-methyl-isoindolin-5-yl)oxyethyl]-1-methyl-imidazole-4-sulfonamide

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

10

- Example A12: N-[2-[3-benzyl-2-(2,2,2-trifluoroacetyl)isoindolin-5-yl]oxyethyl]-1-methyl-pyrazole-4-sulfonamide

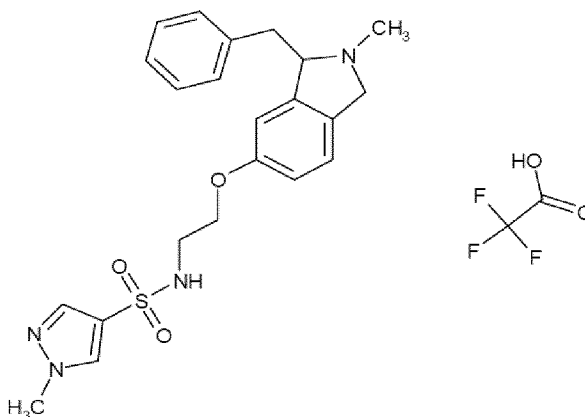


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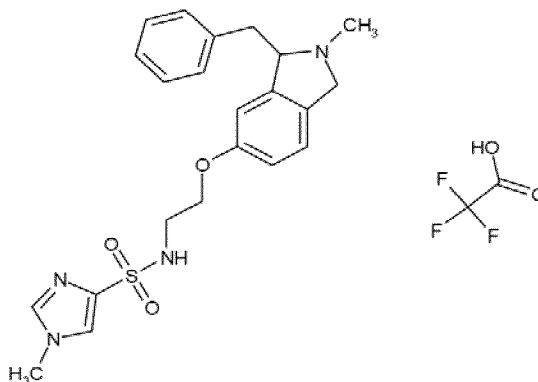
163

ESI-MS $[M+H]^+$ = 509Calculated for $C_{23}H_{23}F_3N_4O_4S$ = 509

- Example A13: N-[2-(3-benzyl-2-methyl-isoindolin-5-yl)oxyethyl]-1-methyl-pyrazole-4-sulfonamide; 2,2,2-trifluoroacetic acid

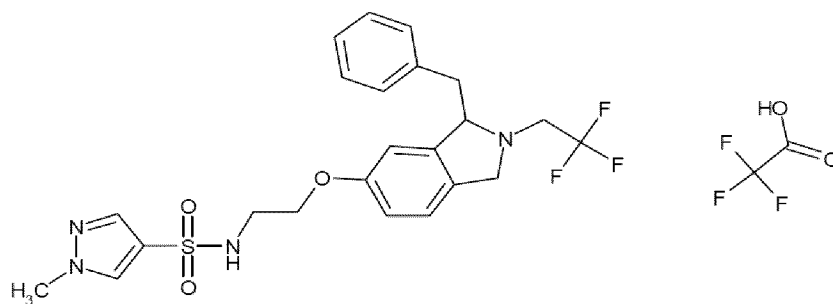
ESI-MS $[M+H]^+$ = 427Calculated for $C_{22}H_{26}N_4O_3S$ = 426

- 10 Example A14: N-[2-(3-benzyl-2-methyl-isoindolin-5-yl)oxyethyl]-1-methyl-imidazole-4-sulfonamide; 2,2,2-trifluoroacetic acid

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

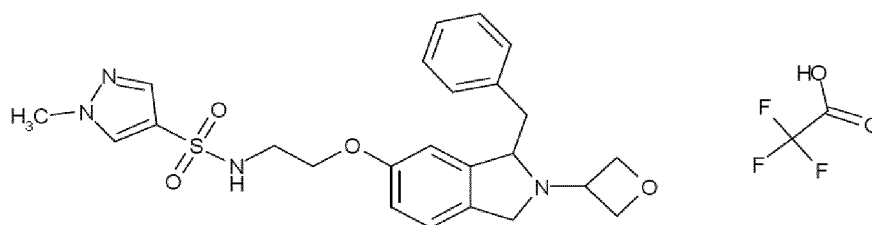
- Example A15: N-[2-[3-benzyl-2-(2,2,2-trifluoroethyl)isoindolin-5-yl]oxyethyl]-1-methyl-pyrazole-4-sulfonamide; 2,2,2-trifluoroacetic acid

164

ESI-MS $[M+H^+] = 495$ Calculated for $C_{23}H_{25}F_3N_4O_3S = 494$

5

Example A16: N-[2-[3-benzyl-2-(oxetan-3-yl)isoindolin-5-yl]oxyethyl]-1-methyl-pyrazole-4-sulfonamide; 2,2,2-trifluoroacetic acid

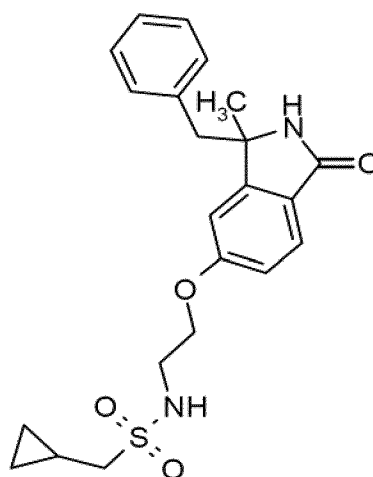


10

ESI-MS $[M+H^+] = 469$ Calculated for $C_{24}H_{28}N_4O_4S = 468$

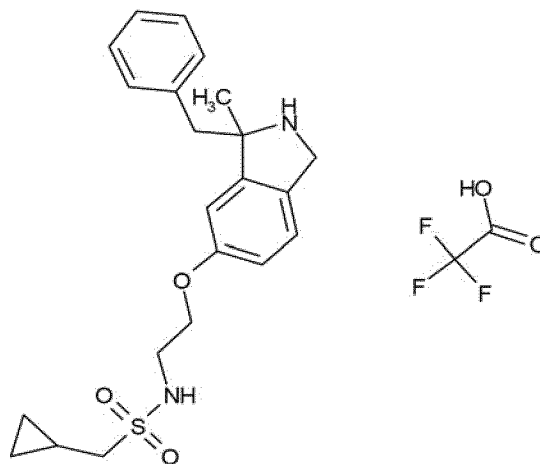
Example A17: N-[2-(3-benzyl-3-methyl-1-oxo-isoindolin-5-yl)oxyethyl]-1-cyclopropyl-methanesulfonamide

15

ESI-MS $[M+H^+] = 415$ Calculated for $C_{22}H_{26}N_2O_4S = 414$

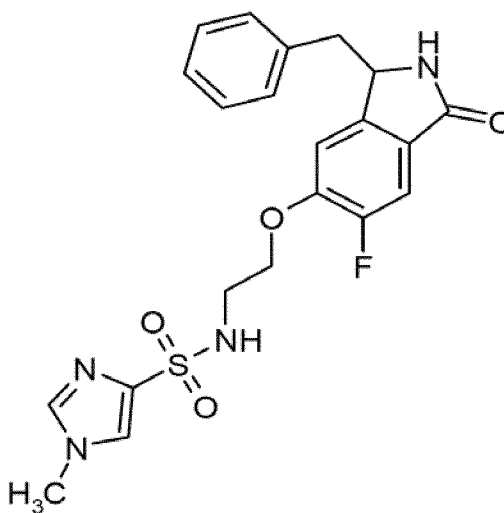
Example A18: N-[2-(3-benzyl-3-methyl-isoindolin-5-yl)oxyethyl]-1-cyclopropyl-methanesulfonamide; 2,2,2-trifluoroacetic acid

5

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

10

Example A19: N-[2-(3-benzyl-6-fluoro-1-oxo-isoindolin-5-yl)oxyethyl]-1-methyl-imidazole-4-sulfonamide

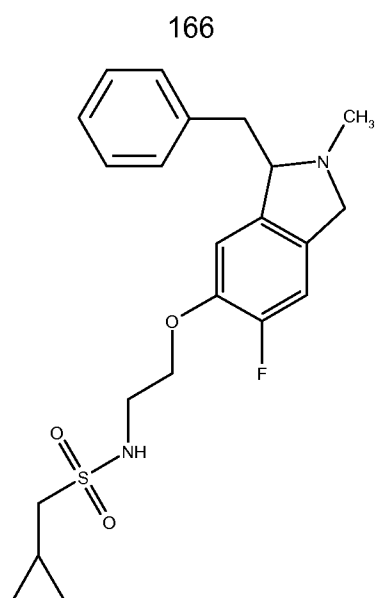


15

ESI-MS $[M+H]^+$ = 443Calculated for $C_{21}H_{21}FN_4O_4S$ = 444

Example A20: N-(2-(3-benzyl-6-fluoro-2-methylisoindolin-5-yloxy)ethyl)-1-cyclopropyl-methanesulfonamide

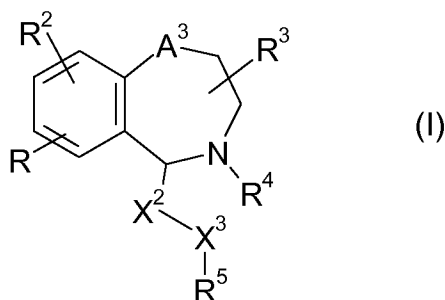
20

ESI-MS $[M+H^+] = 419$ Calculated for $C_{22}H_{27}FN_2O_3S = 418$

We claim:

1. Benzazepine derivatives of the formula (I)

5



wherein

R is R¹-W-A¹-Q-Y-A²-X¹- or -CN;

10

R¹ is hydrogen, C₁-C₆-alkyl, C₃-C₁₂-cycloalkyl-C₁-C₄-alkyl, halogenated C₁-C₆-alkyl, tri-(C₁-C₄-alkyl)-silyl-C₁-C₄-alkyl, hydroxy-C₁-C₄-alkyl, C₁-C₆-alkoxy-C₁-C₄-alkyl, amino-C₁-C₄-alkyl, C₁-C₆-alkylamino-C₁-C₄-alkyl, di-C₁-C₆-alkylamino-C₁-C₄-alkyl, C₁-C₆-alkylcarbonylamino-C₁-C₄-alkyl, C₁-C₆-alkyloxycarbonylamino-C₁-C₄-alkyl, C₁-C₆-alkylaminocarbonylamino-C₁-C₄-alkyl, di-C₁-C₆-alkylaminocarbonylamino-C₁-C₄-alkyl, C₁-C₆-alkylsulfonylamino-C₁-C₄-alkyl, (optionally substituted C₆-C₁₂-aryl-C₁-C₆-alkyl)amino-C₁-C₄-alkyl, optionally substituted C₆-C₁₂-aryl-C₁-C₄-alkyl, optionally substituted C₃-C₁₂-heterocyclyl-C₁-C₄-alkyl, C₃-C₁₂-cycloalkyl, C₁-C₆-alkylcarbonyl, C₁-C₆-alkoxycarbonyl, halogenated C₁-C₆-alkoxycarbonyl, C₆-C₁₂-aryloxycarbonyl, aminocarbonyl, C₁-C₆-alkylaminocarbonyl, (halogenated C₁-C₄-alkyl)aminocarbonyl, C₆-C₁₂-arylaminocarbonyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, optionally substituted C₆-C₁₂-aryl, hydroxy, C₁-C₆-alkoxy, halogenated C₁-C₆-alkoxy, C₁-C₆-hydroxyalkoxy, C₁-C₆-alkoxy-C₁-C₄-alkoxy, amino-C₁-C₄-alkoxy, C₁-C₆-alkylamino-C₁-C₄-alkoxy, di-C₁-C₆-alkylamino-C₁-C₄-alkoxy, C₁-C₆-alkylcarbonylamino-C₁-C₄-alkoxy, C₆-C₁₂-arylcarbonylamino-C₁-C₄-alkoxy, C₁-C₆-alkoxycarbonylamino-C₁-C₄-alkoxy, C₆-C₁₂-aryl-C₁-C₄-alkoxy, C₁-C₆-alkylsulfonylamino-C₁-C₄-alkoxy, (halogenated C₁-C₆-alkyl)sulfonylamino-C₁-C₄-alkoxy, C₆-C₁₂-arylsulfonylamino-C₁-C₄-alkoxy, (C₆-C₁₂-aryl-C₁-C₆-alkyl)sulfonylamino-C₁-C₄-alkoxy, C₃-C₁₂-heterocyclylsulfonylamino-C₁-C₄-alkoxy,

25

C₃-C₁₂-heterocyclyl-C₁-C₄-alkoxy, C₆-C₁₂-aryloxy, C₃-C₁₂-heterocyclyloxy, C₁-C₆-alkylthio, halogenated C₁-C₆-alkylthio, C₁-C₆-alkylamino, (halogenated C₁-C₆-alkyl)amino, di-C₁-C₆-alkylamino, di-(halogenated C₁-C₆-alkyl)amino, C₁-C₆-alkylcarbonylamino, (halogenated C₁-C₆-alkyl)carbonylamino, C₆-C₁₂-arylcarbonylamino, C₁-C₆-alkylsulfonylamino, (halogenated C₁-C₆-alkyl)sulfonylamino, C₆-C₁₂-arylsulfonylamino or optionally substituted C₃-C₁₂-heterocyclyl;

W is -NR⁸- or a bond;

A¹ is optionally substituted C₁-C₄-alkylene or a bond;

Q is -S(O)₂- or -C(O)-;

Y is -NR⁹- or a bond;

A² is optionally substituted C₁-C₄-alkylene, C₁-C₄-alkylene-CO-, -CO-C₁-C₄-alkylene, C₁-C₄-alkylene-O-C₁-C₄-alkylene, C₁-C₄-alkylene-NR¹⁰-C₁-C₄-alkylene, optionally substituted C₂-C₄-alkenylene, optionally substituted C₂-C₄-alkynylene, optionally substituted C₆-C₁₂-arylene, optionally substituted C₆-C₁₂-heteroarylene or a bond;

X¹ is -O-, -NR¹¹-, -S-, optionally substituted C₁-C₄-alkylene, optionally substituted C₂-C₄-alkenylene, optionally substituted C₂-C₄-alkynylene;

R² is hydrogen, halogen, C₁-C₆-alkyl, halogenated C₁-C₄-alkyl, hydroxy-C₁-C₄-alkyl, -CN, C₂-C₆-alkenyl, C₂-C₆-alkynyl, optionally substituted C₆-C₁₂-aryl, hydroxy, C₁-C₆-alkoxy, halogenated C₁-C₆-alkoxy, C₁-C₆-alkoxycarbonyl, C₂-C₆-alkenyloxy, C₆-C₁₂-aryl-C₁-C₄-alkoxy, C₁-C₆-alkylcarbonyloxy, C₁-C₆-alkylthio, C₁-C₆-alkylsulfinyl, C₁-C₆-alkylsulfonyl, aminosulfonyl, amino, C₁-C₆-alkylamino, C₂-C₆-alkenylamino, nitro or optionally substituted C₃-C₁₂-heterocyclyl, or two radicals R² together with the ring atoms of A to which they are bound form a 5- or 6 membered ring;

A³ is -CH₂-, -O-, -NR¹⁶-, or -S-;

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;

R^4 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)NH₂, -C(=NH)NHCN, C_1 - C_6 -alkylsulfonyl, C_6 - C_{12} -arylsulfonyl, amino, -NO or C_3 - C_{12} -heterocyclyl;

X^2 is -O-, -NR⁶-, -S-, >CR^{12a}R^{12b} or a bond;

X^3 is -O-, -NR⁷-, -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 A² and A² is C_1 - C_4 -alkylene or to a carbon atom in X¹ and X¹ 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,

5

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;

10 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 $-NR^{14}-$;

15

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;

20 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 $-NR^{15}-$;

25

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

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

30

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,

C₁-C₆-alkylaminocarbonyl, C₂-C₆-alkenyl, -C(=NH)NH₂, -C(=NH)NHCN, C₁-C₆-alkylsulfonyl, C₆-C₁₂-arylsulfonyl, amino, -NO or C₃-C₁₂-heterocyclyl,

or a physiologically tolerated salt thereof.

5

2. Compound as claimed in claim 1, wherein R is R¹-W-A¹-Q-Y-A²-X¹-.

3. Compound as claimed in claim 1 or 2, wherein -Y-A²-X¹- comprises at least 2, 3 or 4 atoms in the main chain.

10

4. Compound as claimed in any one of claims 1 to 3, wherein R¹ is C₁-C₆-alkyl, C₃-C₁₂-cycloalkyl-C₁-C₄-alkyl, C₃-C₁₂-cycloalkyl, or optionally substituted C₃-C₁₂-heterocyclyl.

5. Compound as claimed in any one of claims 1 to 4, wherein A¹ is a bond.

15

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 -NR⁹-.

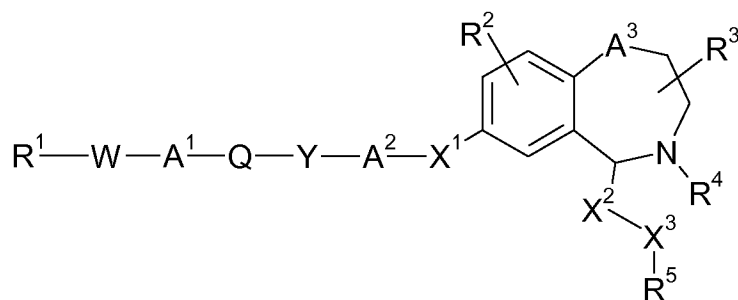
20

8. Compound as claimed in any one of claims 1 to 7, wherein X¹ is -O- and A² is C₁-C₄-alkylene, or X¹ is C₁-C₄-alkylene and A² is a bond.

9. Compound as claimed in any one of claims 1 to 8, wherein R¹-W-A¹-Q-Y-A²-X¹- is R¹-S(O)₂-NR⁹-A²-X¹- or R¹-S(O)₂-X¹-.

25

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

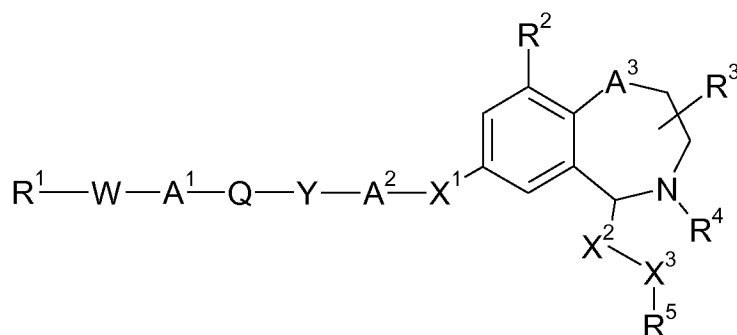
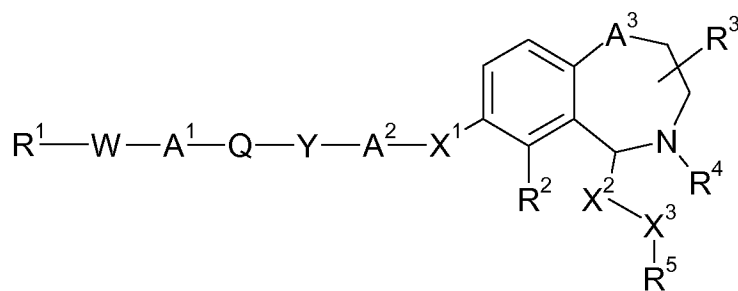
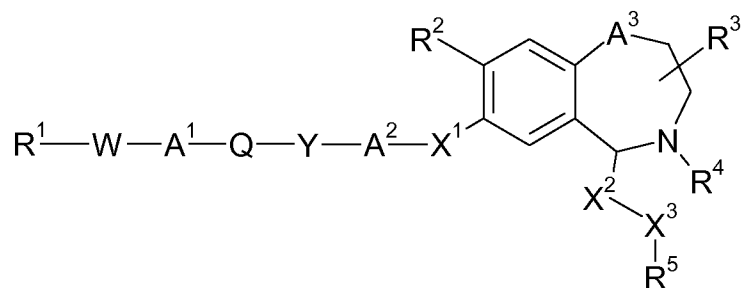


wherein R^1 , W, A^1 , Q, Y, A^2 , X^1 , R^2 , A^3 , R^3 , R^4 , X^2 , X^3 , R^5 are as defined in any one of claims 1 to 9.

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

5

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 , R^4 , X^2 , X^3 , R^5 are as defined in any of claims 1 to 11.

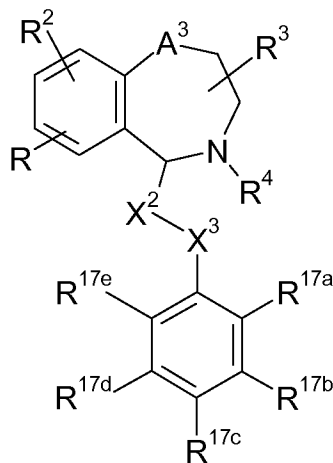
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13. Compound as claimed in any one of claims 1 to 12, wherein A^3 is $-CH_2-$, $-O-$, or $-S-$.

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

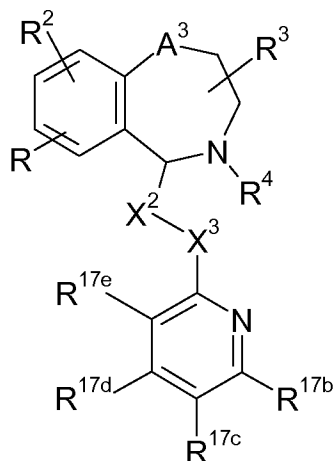
15

15. Compound as claimed in any one of claims 1 to 14, wherein R^4 is hydrogen, C_1 - C_6 -alkyl, or C_3 - C_{12} -cycloalkyl.
16. Compound as claimed in any one of claims 1 to 15, wherein X^2 is $CR^{12a}R^{12b}$.
17. Compound as claimed in any one of claims 1 to 16, wherein X^3 is a bond.
18. Compound as claimed in any one of claims 1 to 17, wherein R^{12a} is hydrogen or C_1 - C_6 -alkyl and R^{12b} is hydrogen or C_1 - C_6 -alkyl.
19. Compound as claimed in any one of claims 1 to 17, wherein R^{12a} , R^{12b} together are optionally substituted C_1 - C_4 -alkylene.
20. Compound as claimed in any one of claims 1 to 19, wherein R^5 is optionally substituted aryl.
21. Compound as claimed in claim 20, having the formula



- wherein R , R^2 , A^3 , R^3 , R^4 , X^2 , X^3 are as defined in any one of claims 1 to 20; and R^{17a} , R^{17b} , R^{17c} , R^{17d} , R^{17e} independently are hydrogen, halogen, or halogenated C_1 - C_6 -alkyl.
22. Compound as claimed in claim 20, having the formula

174



wherein R, R², A³, R³, R⁴, X², X³ are as defined in any one of claims 1 to 20; and
 R^{17b}, R^{17c}, R^{17d}, R^{17e}

independently are hydrogen, halogen, or halogenated C₁-C₆-alkyl.

5

23. Compound as claimed in any one of claims 1 to 22, wherein R⁹ is hydrogen or alkyl; or
 R⁹ is C₁-C₄-alkylene that is bound to a carbon atom in X¹ and X¹ is C₁-C₄-alkylene.

24. Compound as claimed in claim 1, wherein

10

R is R¹-W-A¹-Q-Y-A²-X¹-;

R¹ is C₁-C₆-alkyl, C₃-C₁₂-cycloalkyl-C₁-C₄-alkyl, C₃-C₁₂-cycloalkyl, or optionally substituted C₃-C₁₂-heterocyclyl;

15

W is a bond;

A¹ is a bond;

20

Q is -S(O)₂-;

Y is -NR⁹- or a bond;

A² is C₁-C₄-alkylene;

25

X¹ is -O- or C₁-C₄-alkylene;

R^2 is hydrogen or halogen;

A^3 is $-CH_2-$, $-O-$, $-NR^{16}$, or $-S-$;

5

R^3 is hydrogen;

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

10

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

X^3 is a bond;

R^5 is optionally substituted phenyl or pyridyl;

15

R^9 is hydrogen or alkyl; 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;

20

R^{12a} is hydrogen; and

R^{12b} is hydrogen; or

R^{12a} , R^{12b}

25

together are C_1-C_4 -alkylene; and

R^{16} is hydrogen or C_1-C_6 -alkyl.

25. Compound as claimed in claim 1 which is:

30

N-(2-(1-Benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)ethyl)-1-methyl-1H-imidazole-4-sulfonamide;

N-(2-(1-Benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)ethyl)-1-methyl-1H-pyrazole-4-sulfonamide

- N-(2-(1-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)ethyl)-1-cyclopropylmethanesulfonamide;
- 1-Methyl-1H-imidazole-4-sulfonic acid [2-(1-benzyl-2-methyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)-ethyl]-amide;
- 5 1-Methyl-1H-pyrazole-4-sulfonic acid [2-(1-benzyl-2-methyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)ethyl]-amide;
- Propane-1-sulfonic acid [2-(1-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)-ethyl]-amide;
- Ethanesulfonic acid [2-(1-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)-ethyl]-amide;
- 10 Propane-1-sulfonic acid (1-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]-azepin-8-ylmethyl)-amide;
- Ethanesulfonic acid (1-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]-azepin-8-ylmethyl)-amide;
- N-(1-Benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-C-cyclopropyl-methanesulfonamide;
- 15 1-Methyl-1H-imidazole-4-sulfonic acid (1-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-amide;
- 1-Methyl-1H-pyrazole-4-sulfonic acid (1-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-amide;
- 20 1-Methyl-1H-imidazole-4-sulfonic acid (1-benzyl-2-methyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-amide;
- 1-Methyl-1H-pyrazole-4-sulfonic acid (1-benzyl-2-methyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-amide;
- 1-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepine-8-carbonitrile;
- 25 N-[2-(1-Benzyl-7-fluoro-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)-ethyl]-C-cyclopropyl-methanesulfonamide;
- Propane-1-sulfonic acid [2-(1-benzyl-7-fluoro-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy)-ethyl]-amide;
- Ethanesulfonic acid [2-(1-benzyl-7-fluoro-2,3,4,5-tetrahydro-1H-benzo-[c]azepin-8-yloxy)-ethyl]-amide;
- 30 Propane-1-sulfonic acid (1-benzyl-7-fluoro-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-amide;
- Ethanesulfonic acid (1-benzyl-7-fluoro-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-amide;

- N-(1-Benzyl-7-fluoro-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-C-cyclopropyl-methanesulfonamide;
- 1-Methyl-1H-imidazole-4-sulfonic acid (1-benzyl-7-fluoro-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-amide;
- 5 1-Methyl-1H-pyrazole-4-sulfonic acid (1-benzyl-7-fluoro-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-amide;
- Propane-1-sulfonic acid {2-[1-(4-fluoro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy]-ethyl}-amide;
- Ethanesulfonic acid {2-[1-(4-fluoro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy]-ethyl}-amide;
- 10 1-Methyl-1H-imidazole-4-sulfonic acid [1-(4-fluoro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl]-amide;
- Propane-1-sulfonic acid [1-(4-chloro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl]-amide;
- 15 Ethanesulfonic acid [1-(4-chloro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl]-amide;
- N-[1-(4-Chloro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl]-C-cyclopropyl-methanesulfonamide;
- 1-Methyl-1H-imidazole-4-sulfonic acid [1-(4-chloro-benzyl)-2,3,4,5-tetrahydro-1H-benzo-
- 20 [c]azepin-8-ylmethyl]-amide;
- 1-Methyl-1H-pyrazole-4-sulfonic acid [1-(4-chloro-benzyl)-2,3,4,5-tetrahydro-1H-benzo-[c]azepin-8-ylmethyl]-amide;
- Propane-1-sulfonic acid (1-pyridin-2-yl-methyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-amide;
- 25 Ethanesulfonic acid (1-pyridin-2-yl-methyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-amide;
- C-Cyclopropyl-N-(1-pyridin-2-ylmethyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl)-methanesulfonamide;
- 1-Methyl-1H-imidazole-4-sulfonic acid {2-[1-(4-chloro-benzyl)-2,3,4,5-tetrahydro-1H-
- 30 benzo[c]azepin-8-yloxy]-ethyl}-amide;
- 1-Methyl-1H-pyrazole-4-sulfonic acid {2-[1-(4-chloro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy]-ethyl}-amide;
- 1-Methyl-1H-imidazole-4-sulfonic acid {2-[1-(3-chloro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy]-ethyl}-amide;

1-Methyl-1H-pyrazole-4-sulfonic acid {2-[1-(3-chloro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy]-ethyl}-amide;

1-Methyl-1H-imidazole-4-sulfonic acid {2-[1-(3-fluoro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy]-ethyl}-amide;

5 1-Methyl-1H-pyrazole-4-sulfonic acid {2-[1-(3-fluoro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yloxy]-ethyl}-amide;

Propane-1-sulfonic acid [1-(4-fluoro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl]-amide;

10 Ethanesulfonic acid [1-(4-fluoro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl]-amide;

C-Cyclopropyl-N-[1-(4-fluoro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl]-methanesulfonamide;

1-Methyl-1H-imidazole-4-sulfonic acid [1-(4-fluoro-benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ylmethyl]-amide.

15 or a physiologically tolerated salt thereof.

26. The compound as claimed in any one of claims 1 to 25 for use in therapy.

20 27. Pharmaceutical composition which comprises a carrier and a compound of any one of claims 1 to 25.

28. 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 25.

25 29. The use of a compound of any one of claims 1 to 25 in the manufacture of a medicament for inhibiting the glycine transporter GlyT1.

30 30. 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 25.

31. The use of a compound of any one of claims 1 to 25 in the manufacture of a medicament for treating a neurologic or psychiatric disorder or pain.

32. The compound of any one of claims 1 to 25 for use in a method of treating a neurologic or psychiatric disorder or pain.

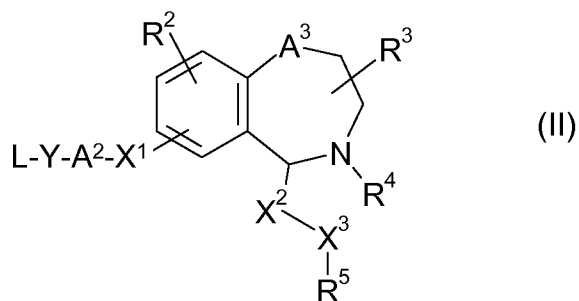
5 33. The method, use or compound as claimed in any one of claims 35 to 39, wherein the disorder is associated with glycinergic or glutamatergic neurotransmission dysfunction.

34. The method, use or compound as claimed in any one of claims 30 to 33, wherein the neurologic disorder is a cognitive disorder such as dementia, cognitive impairment, at-
10 tention deficit disorder.

35. The method, use or compound as claimed in claim 34, wherein the attention deficit disorder is a the attention deficit disorder with hyperactivity.

15 36. The method, use or compound as claimed in any one of claims 30 to 33, wherein the psychiatric disorder is an anxiety disorder, a mood disorder such as depression, a bipolar disorder, schizophrenia, or a psychotic disorder.

37. Benzazepines derivatives of formula (II)



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wherein L is an amino-protecting group, Y is NR⁹, and A², X¹, R², A³, R³, R⁴, X², X³, R⁵ are defined as in any one of claims 1 to 25.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/058760

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D223/16 C07D267/14 C07D403/12 C07D413/12 A61K31/55
A61K31/553 A61P25/24

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 A61K A61P

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, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2009/121872 A2 (ABBOTT GMBH) 8 October 2009 (2009-10-08) page 1, line 6 - page 2, line 9; claims; examples	1-37
Y	----- US 2007/021408 A1 (SAMID) 25 February 1997 (1997-02-25) page 9, paragraph 26 - paragraph 28; claims; examples 17, 19, 20, 23, 70, 81, 91, 93,	1-37
A	----- WO 2008/038053 A1 (LECTUS THERAPEUTICS) 3 April 2008 (2008-04-03) page 1 - page 4; claims; examples ----- -/-	1-37



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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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

20 August 2012

Date of mailing of the international search report

27/08/2012

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/058760

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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A	EP 2 246 331 A1 (WESTFÄLISCHE WILHELMS UNIVERSITÄT MÜNSTER) 3 November 2010 (2010-11-03) page 1, paragraph 1 - paragraph 5; claims; examples -----	1-37

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Information on patent family members

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